

Enhanced anti-tumor efficacy of Electrochemotherapy combined with marginal surgery in dogs with Mast Cell Tumors and Soft Tissue Sarcomas

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Abstract

Background and Objectives

Electrochemotherapy (ECT) has emerged as an effective treatment modality for various tumor types in both preclinical and clinical settings within human and veterinary Oncology. We sought to evaluate the effect of electrochemotherapy (ECT) on survival of companion dogs with mast cell tumors and soft tissue sarcomas as an adjuvant to surgery.

Materials and Methods

A single-institution retrospective case series evaluation was used to identify dogs with mast cell tumors and soft tissue sarcomas undergoing surgical resection followed by electrochemotherapy from 2020–2024. Patients were selected based on having both therapies and categorized by histopathology. ECT was combined post-surgery with IV bleomycin and IL cisplatin in all cases. Overall response rate, survival and recurrence was analyzed.

Results

A total of 605 patients were identified as having surgery with incomplete margins followed by electrochemotherapy with either a diagnosis of mast cell tumor or soft tissue sarcoma. Grade was determined for all patients and recurrence free survival was stratified according to grade. Three hundred thirty-one dogs with mast cell tumor were retrospectively evaluated and two hundred and seventy-four dogs with soft tissue sarcoma were evaluated. This study obtained local control in both cutaneous and subcutaneous mast cell tumors as well as soft tissue sarcomas. The mean progression free interval in cutaneous mast cell tumors was 1825 days for grade I, 1803 days for low grade II, 902 days for high grade II and 817 days for grade III. Subcutaneous mast cell tumors were evaluated to be 1814 days for low grade and 1180 days for high grade. The mean progression free interval soft tissue sarcomas were 1432 days for grade I, 1000 days in grade II and 551 days in grade III respectively. Necrosis was observed at an average rate of 22% in mast cell tumors and in 18% of soft tissue sarcomas.

Conclusion

In this large study, electrochemotherapy decreased local recurrences after incomplete resection from surgery. The majority of publications are from European countries and this is the first evaluation of a large cohort of cases from the United States able to define overall progression free interval according to grade. Electrochemotherapy can offer a localized mechanism of control with minimal toxicity and continued use of this therapy is warranted in other tumor types.

Introduction

Mast cell tumors (MCTs) and soft tissue sarcomas (STSs) are among the most common cutaneous and subcutaneous tumors in dogs, together representing a significant proportion of surgically managed skin

tumors. Combined, canine mast cell tumors and sarcomas constitute 70%-80% of all skin tumors. (1,2) The role of surgery in treatment of both mast cell tumors and sarcoma is well-defined(1,3–6). The primary goals of treatment remain long-term survival, local control, and functional preservation. With improved multimodality therapy, widespread use of marginal-excision surgery has become the foundation of curative-intent surgical management for these patients. Strategies to enhance local tumor control in both diseases have most commonly relied on combining surgery with adjuvant treatments, including radiation therapy (7) (8–11), occasionally supplemented with hyperthermia (12), adjuvant chemotherapy(13–16), or electrochemotherapy (ECT) (17–19)

Both tumor types exhibit considerable variation in biological behavior, ranging from locally invasive to those with aggressive or metastatic potential. Local recurrence in soft tissue sarcoma is 10 times more likely in dogs with incomplete resection compared with dogs with clean margins (20,23).

Low- and intermediate-grade MCTs, as classified by the Patnaik or Kiupel systems(21,22), and most STSs typically demonstrate slow growth and locally infiltrative behavior, causing morbidity primarily through local tissue invasion rather than distant metastasis. (3,5,6,23) Similar to MCTs, the prognosis for STSs depends on histologic grade, completeness of excision, and biological markers of proliferation and malignancy. Additional prognostic factors—including tumor size, anatomic location, clinical stage, and specific molecular alterations—further influence recurrence and metastatic risk in both tumor types. (1,3–6)

Wide surgical excision remains the primary treatment for localized MCTs and STSs and is usually curative when tumor-free margins are achieved. However, achieving adequate margins may be difficult in regions with limited skin or complex anatomy such as the head or distal limbs (1,3,5,6,21–22). Several studies have reported excellent outcomes for low- to intermediate-grade MCTs and low-grade STSs even with incomplete margins,(1,23–26) making the routine use of adjuvant therapy controversial due to the potential for overtreatment.

Use of adjuvant therapy after surgery in both diseases depends on an overall assessment of risk for local recurrence. Risk is based on the complex interplay of patient and tumor factors. The histopathologic subtype, anatomic site, tumor grade, size, adjacent critical normal structures, the ability to obtain a negative margin oncologic resection and owners desires all determine whether additional therapy should be pursued after surgery.

The clinical management of incomplete margins should be based on both clinical and histopathologic evaluations. Owners often would pursue adjuvant therapy if it is minimally invasive and limited in number of sessions even in an older patient, making electrochemotherapy an ideal option for these patients. Most patients received surgery and 1 session of electrochemotherapy for low-grade tumors (69% surgery with 1 session of ECT vs 31% surgery with 2 sessions of ECT). Penetration is not cell-type dependent. Tumors of many histology can be treated with very good results, with an objective response rate of around 85–100%. This high response rate can be observed in dogs, cats, horses, and of course in human patients as well. (7,29)

Materials and Methods

Animal selection: Between January 2020 and December 2024, 605 dogs were treated with surgery and electrochemotherapy for mast cell tumors or soft tissue sarcomas. The dogs had been referred to a tertiary care veterinary facility as they either had recurrent tumors or anticipated difficult surgical planning. Eligibility criteria also included animals with normal blood tests and chemistries and no radiographic or ultrasonographic visible metastasis.

Study Design:

To evaluate the anti-tumor effectiveness of electrochemotherapy in the post-operative setting after incomplete surgical resection. Electrochemotherapy was performed on scars approximately 2 weeks after surgical healing. Both naïve and recurrent patients were considered provided macroscopic disease was marginally excised again with a board certified surgeon prior to ECT.

Electrochemotherapy treatment: All mast cell tumor patients were recommended to start oral 1-2mg/kg twice daily dosing of diphenhydramine (Microlabs Limited, Bangalore, India) at home before the first electrochemotherapy session and counseled to remain on the medication for at least 2 weeks after the last session.

Before treatment with electrochemotherapy, all dogs have an IV catheter placed and are premedicated with IV 0.2mg/kg butorphanol (Dolorex, Merck, Madison, NJ, USA) and IV 0.1mg/kg midazolam (Hospira Inc, Lake Forest, IL, USA). Anesthesia was induced with IV 4-6mg/kg IV to effect propofol (Hospira Inc, Lake Forest, IL, USA; Sagent, Schaumburg, IL, USA) or IV 2mg/kg Alfaxalone (Alfaxan, Zoetis, Kalamazoo, MI, USA) and patients were intubated and maintained on Isoflurane (Isospore, Dechra, Overland Park, KS, USA).

Electrochemotherapy consisted of Intravenous administration of Bleomycin (Kindos Pharmaceuticals, Memphis, TN, USA) with a period of wait time of 4 minutes and an intralesional administration into the scar of cisplatin (Teva Pharmaceuticals, North Wales, PA, USA). Cisplatin is commercially available in an aqueous concentration of 1mg/ml. The total dose of calculated drug for each patient maxed out at 15000IU/m². All patients were treated by one clinician to minimize variation in the dosing. The average calculation of the dose was given as an approximate 2:1 ratio of Bleomycin IV and cisplatin IL administration into the scar. This protocol was decided upon based on experience by the clinician between 2010 and 2015 treating these same tumor types as well as historic literature.

The protocol for both MCT and STS is to calculate a maximum dose of 15IU/m² for the patient. This is split between Bleomycin IV and cisplatin IL at an approximately 2/3 ratio. The scar is treated approximately 4 minutes later with an OnkoDisruptor clinical electroporation device with modified caliper electrodes: 8 biphasic waveforms; pulses duration of 100 µs ; pulse repetition frequency of 1 Hz and pulse amplitude 1200 volts/cm. The scar was treated with a minimum of 2cm of distance further than the surgical undermining of the tissues and guided by remaining sutures placed by the surgeon in many

cases. Good contact with the skin was achieved by shaving the patient and application of conductive gel to the treatment area. During the ECT sessions, the patients were monitored using a pulse oximeter.

Treatment evaluation:

After treatment, the patients were kept in the hospital for 2–4 hours. Response to treatment and local toxicity were assessed prior to the second therapy (when performed) or every three to four months thereafter. After the second treatment, thoracic radiographs and abdominal ultrasonography were performed according to clinician preference to monitor progression for high grade tumors. Side effects of ECT were evaluated following each ECT treatment and were graded using the Veterinary Cooperative Oncology Group–Common Terminology Criteria for Adverse Events (VCOG-CTCAEv2) (27). Response to treatment was evaluated through physical exam and estimated using the median time to terminal event and its 95% confidence interval. Survival analysis was estimated according to the Kaplan-Meier method (28). The terminal event was recurrence or death attributable to cancer or other non-cancer causes. Statistical analysis tested for any relationship between tumor response and site, tumor histotype, prior surgery and duration of symptoms prior to therapy. Statistical analysis was performed using SigmaPlot software (version 15.0 Grafiti LLC; Palo Alto, CA, USA).

Results

There was a total of 332 mast cell tumors, divided into cutaneous and subcutaneous and a total of 274 soft tissue sarcomas as shown in Figure 1. Figure 1 – Breakdown of Histopathologic grades of cutaneous and subcutaneous mast cell tumors and soft tissue sarcomas (original data).

One dog was treated with both a low grade soft tissue sarcoma and a cutaneous grade II low grade mast cell tumor. We evaluated both cutaneous and subcutaneous mast cell tumors and calculated the overall progression free interval (PFI) at the level of the scar in each grade.

With grade I cutaneous mast cell tumors, the median progression free interval was not reached, the mean was 1825 days (CI 1533 -2117 days). In grade II low grade mast cell tumors, the median progression free interval was not reached and the mean was 1803 days (CI 1678 – 1927 days). In grade II high grade mast cell tumors, the median progression free interval was 1120 days, the mean 902 days (CI 655 – 1149 days). Lastly, the grade III mast cell tumors median PFI was not reached and the mean was 817 days (CI 547- 1087 days) as shown in Figure 2.

Subcutaneous mast cell tumors were also evaluated and categorized based on low and high designation on histopathology. Low grade subcutaneous mast cell tumors median PFI was not reached with a mean 1814 days (CI 1554 – 2074 days). In high grade subcutaneous mast cell tumors, the median PFI was not reached, mean 1180 days (CI 675 – 1684 days) as shown in Figure 3.

Soft tissue sarcomas were categorized in three groups based on standard grading scheme. Low grade soft tissue sarcomas median PFI was not reached with a mean 1432 days (CI 1281 – 1583 days).

Intermediate grade soft tissue sarcomas had a median PFI of 896 days with a mean 1000 days (CI 812 – 1189 days). High grade soft tissue sarcomas had a median PFI of 420 days, mean 551 days (CI 321 – 782 days) as shown in Figure 4.

Local recurrence was present after ECT in cutaneous mast cell tumors: grade I (3 of 24, 13% of cases at a median of 516 days) low grade II (13 of 163, 8% of cases at a median of 400 days), high grade II (8 of 24, 33% of cases at a median of 353 days), grade III (6 of 19, 31% of cases at a median of 257 days) and subcutaneous mast cell tumors: low grade (14 of 88, 16% of cases at a median of 654 days) and high grade (4 of 14, 28% of cases at a median of 130 days). The local recurrence rates after ECT in sarcomas for Grade I (23 of 143, 16% of cases at a median of 582 days), grade II (25 of 115, 22% of cases at a median of 507 days) and grade III (8 of 16, 50% of cases at a median of 276 days) respectively.

Treatment tolerance: There were no serious local or general adverse effects noted. Muscle contractions were observed after application of each pulse and depending on the tissue treatment may cause a visible contraction of the treated limb or body region. The contractions are instantaneous and disappear at the end of each pulse. The intralesional treatment of cisplatin into the skin did not result in any local or systemic toxicosis except for minor occasional bleeding from insertion of the needle. After treatment, in some cases, partial necrosis of the tumors was observed within the first week and peaked between Day 5-10 after treatment. This was more commonly observed in mast cell tumor patients where diphenhydramine was not being given by the owners or in higher grade tumors. In these cases, the second treatment was delayed if not healed well. Necrosis was noted in cutaneous mast cell tumors: grade I (3 of 24, 13%) low grade II (23 of 163, 14%), high grade II (8 of 24, 33%), grade III (6 of 19, 31%) and subcutaneous mast cell tumors: low grade (18 of 88, 20%) and high grade (3 of 14, 21%). Necrosis also occurred in soft tissue sarcomas in grade I (21 of 143, 15%), grade II (23 of 115, 20%) and grade III (3 of 16, 18%). Full healing was usually complete by the 4th week after treatment. This cutaneous toxicity was also most common overlying joints or in thin skinned areas (toe webbing, eyelid) in both mast cell tumors and soft tissue sarcomas.

Discussion

To the best of our knowledge, this is the first study of a large cohort of adjuvant ECT in dogs with STS and MCT in the United States. ECT coupled with surgery resulted in complete remission in more than 75% of our patients (282 out of 332 MCT, 215 out of 274 STS achieved CR) as evaluated by monitoring exams at every 3–6-month intervals. This study obtained local control in excess of 300 days in 223 out of 332 mast cell tumors (67%) and in 170 out of 264 sarcomas (62%). The choice of offering ECT paired with surgery was based on our previous experience with the procedure and the lack of external beam radiation therapy in our area. Because both incompletely resected mast cell tumors and soft tissue sarcomas have risk for local recurrence, additional therapy to invest in the surgical scar was recommended in these cases. There is debate on whether additional therapy is warranted after surgical resection of cutaneous tumors of a low grade nature. The desired pursuit of additional therapy for tumor

control was many times driven by owner objectives, monetary abilities and ease of a few additional sessions.

Overall, our results of median time to recurrence compares highly favorable to other studies performed across the globe. Additionally, this helps to validate that even low grade subcutaneous mast cell tumors can rival cutaneous mast cell tumors in their control with this therapy suggesting that electrochemotherapy penetrates deep enough to cover this unique subset of mast cell disease. Penetration is also not cell-type dependent. Tumors of many histology can be treated with very good results, with an objective response rate of around 85–100%.

High grade II and grade III mast cell disease also did well with this therapy in achieving local control. Electrochemotherapy is a local therapy and progression free interval at the level of the scar was the main driver for evaluation in these patients. Given the risk for metastasis in these patients, the majority went on to have traditional IV chemotherapy or a tyrosine kinase inhibitor for systemic coverage. Recognizing it is challenging to isolate the individual effects of two concurrent treatments on overall survival due to potential interactions and overlapping impacts we did not run a survival analysis on these patients. The influence of ECT specifically on the tissues can be more effectively assessed through the endpoint of local disease progression, which provides clearer insight into its specific contribution. Given the recent advancements of electrochemotherapy paired with immunotherapy and small molecule inhibitors it is possible that a synergy was seen in these patients prior to this discovery.

Mast cell tumors should be on diphenhydramine when they receive ECT and continue that diphenhydramine for at least 2 weeks after the last session of ECT. The rate of degranulation / necrosis from ECT does appear to be related to grade in all mast cell disease. At least 30% of higher grade mast cell tumors are likely to have degranulation after electrochemotherapy and may benefit from additional intervention with steroids

In general, it is well accepted that dogs with high grade STS are prone to recurrence within 4–6 months in case of incomplete excision (4,17–20,29). This data suggests that we can benefit half of these patients with only two sessions of additional anesthesia after marginal excision for 14 months and those that only partially respond can get 9 months. This marginal excision was performed by a board-certified surgeon as a cytoreductive surgery with the goal of no gross disease present and to facilitate primary closure allowing for electrochemotherapy to proceed in a timely fashion.

These findings suggest that ECT represents a promising therapeutic alternative to radiation therapy for private practices lacking access to a linac as its ease of administration, demonstrated efficacy, minimal systemic toxicity, and relatively low cost render it an appealing modality for the veterinary oncologist. As veterinary medicine moves into more immunotherapy strategies for patients, this will also be a natural pairing to enhance its effect and provide potential abscopal effects in our patients. (30)

This study showed that electrochemotherapy is an effective treatment following incomplete resection for dogs with cutaneous and subcutaneous mast cell tumors as well as soft tissue sarcomas.

Declarations

Acknowledgments

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Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics Declaration: This is a retrospective analysis of outcomes in companion dogs treated in a clinical setting. All clients had signed consent for the procedure of electrochemotherapy with authorization for future research expectations, use of pictures and publication of the clinical data. Since the procedure of electrochemotherapy is a modality that is well described from a technical standpoint, ethical approval was not required or involved.

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Figures

Mast cell tumors

- Cutaneous Grade I – 24
- Cutaneous Grade II low grade – 163
- Cutaneous Grade II high grade – 24
- Cutaneous Grade III – 19
- Subcutaneous low grade – 88
- Subcutaneous high grade – 14

Soft Tissue Sarcomas

- Low grade I – 143
- Intermediate grade II – 115
- High grade III – 16

Figure 1 Caption: A total of 332 mast cell tumors, divided into cutaneous and subcutaneous and a total of 274 soft tissue sarcomas treated with electrochemotherapy.

Figure 1

See image above for figure legend.

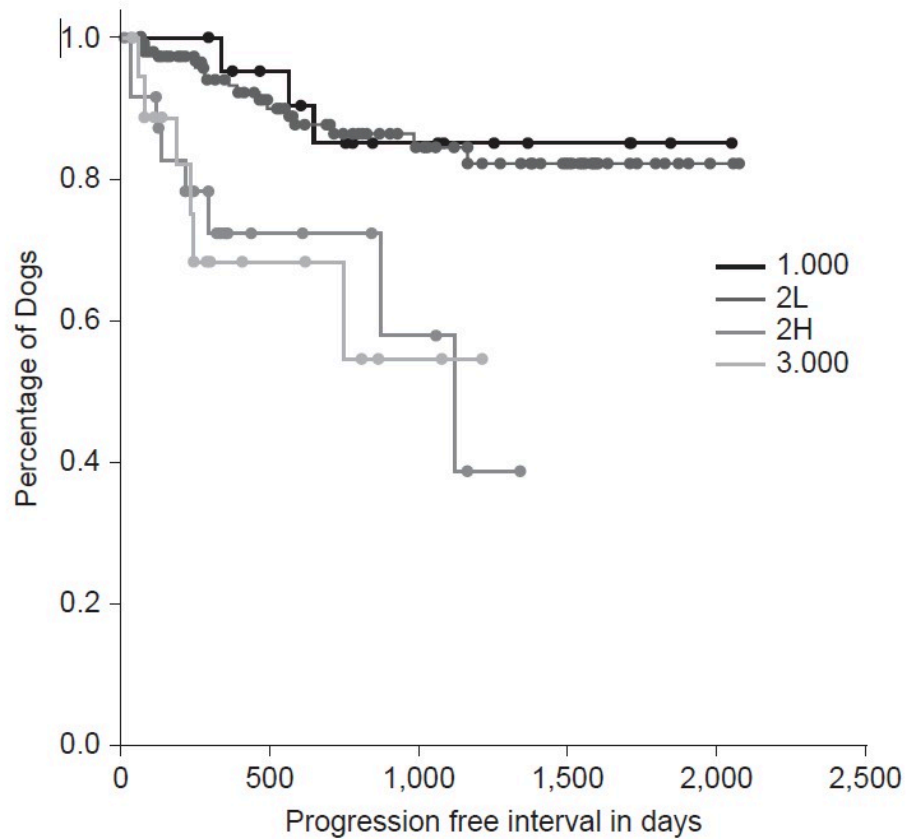


Figure 2 caption: Progression free interval of cutaneous mast cell tumors by grade. Grade I cutaneous mast cell tumors, median PFI not reached; mean PFI 1825 days (CI 1533 – 2117 days). Grade II low grade cutaneous mast cell tumors, median PFI not reached; mean PFI 1803 days (CI 1678 – 1927 days). Grade II high grade mast cell tumors, the median PFI 1120 days; mean PFI 902 days (CI 655 – 1149 days). Grade III cutaneous mast cell tumors, median PFI not reached; mean 817 days (CI 547 – 1087 days)

Figure 2

See image above for figure legend.

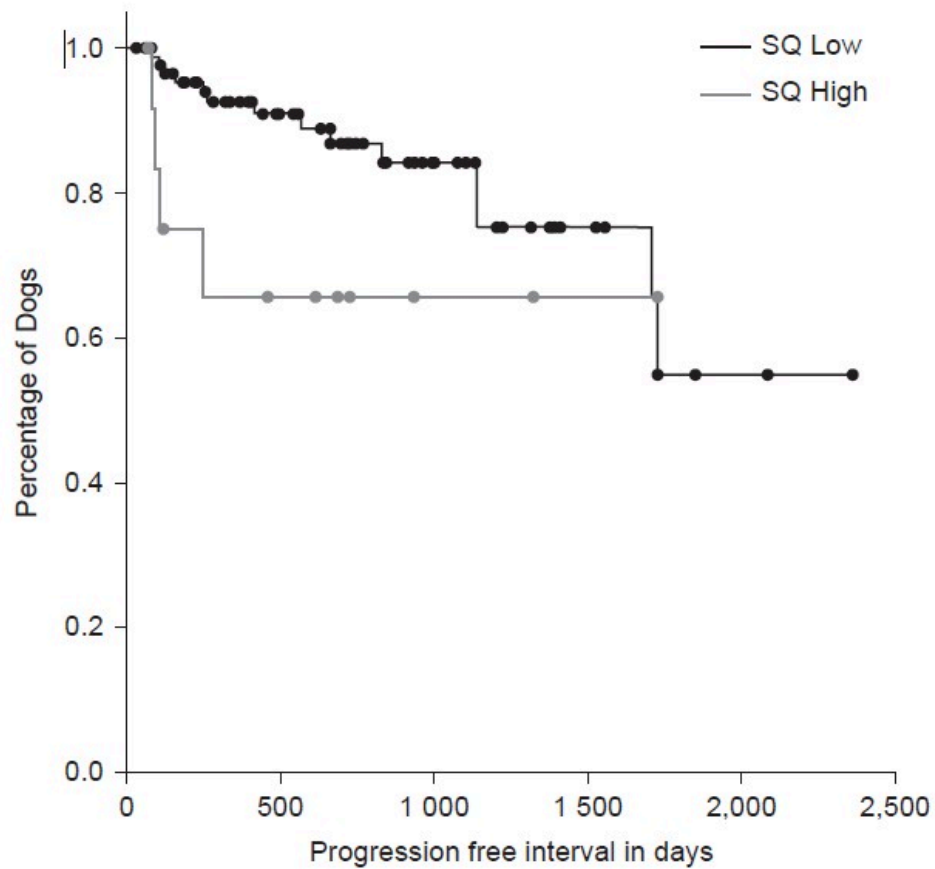


Figure 3 caption: Low grade subcutaneous mast cell tumors, median PFI not reached; mean PFI 1814 days (CI 1554 – 2074 days). High grade subcutaneous mast cell tumors, median PFI not reached; mean PFI 1180 days (CI 675 – 1684 days).

Figure 3

See image above for figure legend.

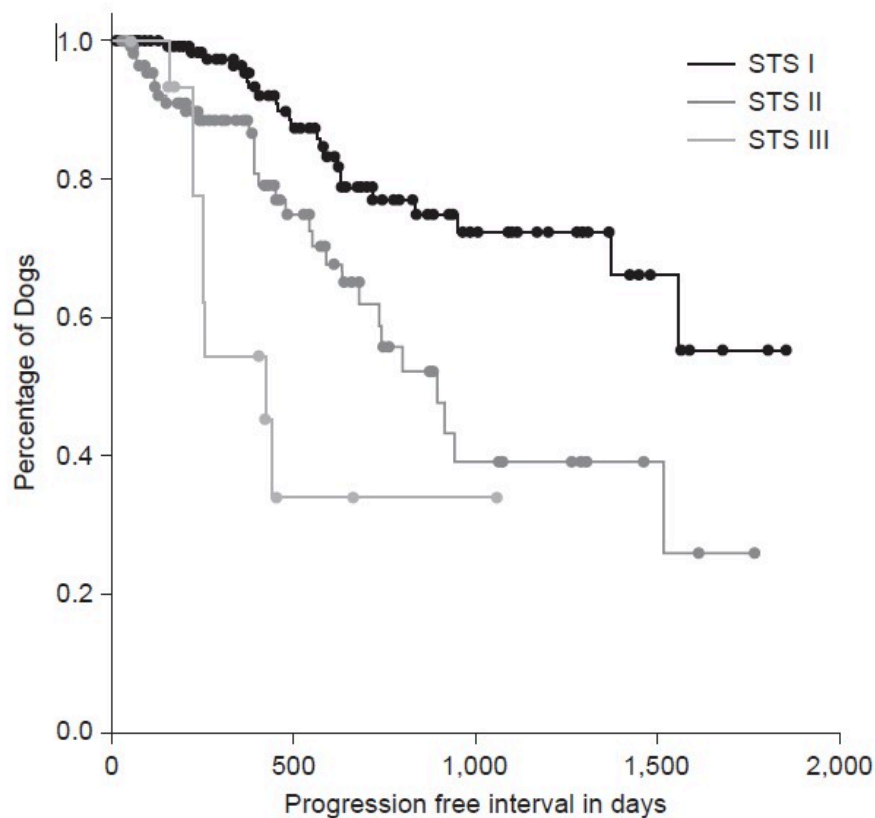


Figure 4 caption: Soft tissue sarcomas. Low grade soft tissue sarcomas, median PFI not reached; mean 1432 days (CI 1281 – 1583 days). Intermediate grade soft tissue sarcomas, median PFI 896 days; mean 1000 days (CI 812 – 1189 days). High grade soft tissue sarcomas, median PFI 420 days; mean 551 days (CI 321 – 782 days).

Figure 4

See image above for figure legend.