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# Correlation of Clinical, Histopathological and Histomorphometric Features of Canine Soft Tissue Sarcomas

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**Abstract**

Soft-tissue sarcomas (STS) represent a heterogeneous group of tumours with similar histological characteristics and biological behaviour. This study aimed to describe the correlation between clinical, histopathological and histomorphometric features of STS in dogs. Medical records were reviewed to identify all dogs in which an STS was diagnosed between 2006-2017. Thirty cases were included, and tumour samples and medical records were recovered. Most of the dogs were mixed breed (40%) and 80% of the STS were located in the subcutaneous connective tissue. Histopathological classification showed that undifferentiated sarcoma (17%) and peripheral nerve sheath tumour (30%) were the most common STS. Grade I STS were obtained in 50% of cases (15/30), and grade II or III tumours compromised 43% (13/30) and 7% (2/30) respectively. The mitotic index ranged from zero to 26 (5.8 ± 7.5). Increased nucleus:cytoplasm ratio was moderately associated with higher tumour grade ($p = 0.05$; $rS = 0.361$) and mitotic index ($p = 0.05$; $rS = 0.355$), while the number of microvessels was positively correlated with degree of differentiation ($p = 0.05$; $rS = 0.362$) and nuclear pleomorphism ($p = 0.036$; $rS = 0.384$). Histomorphometry proved to be useful in the evaluation of STS, representing an additional tool correlated with well-established prognostic factors (histopathological grade, degree of differentiation, nuclear pleomorphism).

**Key words:** oncology, dog, nucleus-cytoplasm ratio, microvessel density.

## Introduction

Soft-tissue sarcomas (STS) represent a heterogeneous group of tumours with similar histological characteristics and biological behaviour (14, 20), with high local recurrence rate (7-75%) and low metastatic potential (1.7-34.6%) (2, 3, 17). Histologically, these tumours are derived from the primitive ectoderm or embryonic mesoderm and can develop in muscles, tendons, ligaments, articular capsules, fascias, nerves, blood and lymphatic vessels (9, 22). Despite their similar origin, they can be classified as to cell differentiation in a variety of histological types, including fibrosarcoma, malignant peripheral nerve sheath tumour (MPNST), hemangiopericytoma, myxosarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma and undifferentiated sarcoma (14, 23).

Histopathological classification has no correlation with the biological behaviour of the disease (3), contrary to what is observed for histopathological grading (2, 3, 9, 25, 26). In general, STSs present a slow and infiltrative growth, through thin projections that often go beyond the pseudocapsule that wraps the tumour, resulting in poorly defined margins (14, 20, 22). Local recurrences occur, after marginal excision, in 7% (3/41) of low-grade tumours and,

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34% (13/41) and 75% (3/4) of intermediate and high-grade tumours, respectively (25). Nevertheless, the metastatic potential is low compared to other malignancies (29), ranging from 1.7-29.5% for low grade tumours and 15-34.6% for high-grade tumours (2, 17).

This particular biological behaviour makes wide or radical surgical excision the most efficient method for treating these tumours (10, 24). However, complete resection can be difficult, considering the infiltrative aspect of these neoplasms and their location (10) and, when necessary, surgery should be combined with local control techniques, such as radiotherapy or electrochemotherapy (24, 33, 34). Margin revision surgeries may also be indicated if they are compromised (8).

The extent of the disease and histopathological grading are useful to guide therapeutic decisions (31). These tumours have little response to chemotherapy, and while metronomic chemotherapy might be recommended for cases with incomplete resection, in order to increase disease-free-interval (4, 13, 29), maximum tolerated dose chemotherapy mainly using doxorubicin, might me applied for high-grade tumours and metastatic disease (3, 6).

In dogs, STS often develop in the subcutaneous tissue and represent 9-15% of all cutaneous/subcutaneous tumours in this species (9, 12, 22), besides, it occurs more frequently in middle-aged to elderly animals, with no predisposition for breed or gender (21). In humans, STS are considered to be rare tumours in adults, however, they represent about 6% of all malignant neoplasms in young people under the age of fifteen, and the fifth leading cause of cancer death in this age group (19). Understanding the biological behaviour of the disease in dogs can help understanding the disease in humans and vice versa, and comparative study is important especially if we consider the close relationship established between dogs and their guardians, with exposure to the same environmental carcinogens, since they share the same daily life, eating habits, lifestyle and even states of emotional stress.

This study aimed to describe the correlation between clinical, histopathological and histomorphometric features of STS in dogs, aiming to improve the understanding of their biological behaviour.

## Material and methods

This retrospective study included 30 samples of canine STS registered at the Pathology Laboratory of the Veterinary Hospital Professor Alexandre Hippler of the University of Vila Velha (Espirito Santo, Brazil), between January of 2006 and December of 2017. Medical records were recovered for gathering information related to patient identification (age, breed, sex and weight), clinical presentation of the tumour (size, presence of ulceration), as well as the location and therapeutic conduct. Owners were contacted by phone to complement missing information on the medical records, with emphasis on the disease-free interval and overall survival, estimated from the date of surgery (for disease-free interval and survival) and/or diagnosis (for survival). It was observed a median overall survival of 509 days.

Clinical staging was performed based on clinical examination and auxiliary diagnostic tests (aspiration cytology, thoracic radiography, abdominal ultrasound and in some cases, computed tomography), in order to describe in detail, the extent of the disease both locally and at a distance.

The paraffin blocks were revised from 5 μm histological sections. The slides were stained with haematoxylin and eosin (HE), Gomori trichrome, for quantification of muscle fibers and collagen, and Alcian blue for identification of matrix mucin.

Tumours were classified according to the criteria of the World Health Organization and graded according to the system proposed by Trojani et al. (1984) for STS in humans, also used in canine species (9, 19, 25). The criteria used in this study are summarized in table 1, and include cell differentiation, mitotic index and necrosis percentage.

After tumour fixation the surgical margins were marked with India ink. These margins were evaluated histologically regarding the presence or absence of tumour cells from the primary tumour. Free margins were defined when tumour cells were not observed and compromised or infiltrated when the stained margins presented the same cells as the primary tumour.

For histomorphometric analysis, using a light photomicroscope five images were obtained from each tumour sample, being the captured image obtained from

**Table 1.** Grading system used for soft tissue sarcomas in dogs (adapted from Trojani et al, 1984 and Dennis et al, 2011).

| Score | Cell diferentiation | Necrosis | Mitotic figures (in 10 high-power-fields) |
|---|---|---|---|
| 1 | Resembles normal adult mesenchymal tissue | None | 0-9 |
| 2 | Specific histological subtype, however, the differentiation is poor | ≤50% necrosis | 10-19 |
| 3 | Undifferentiated tumour | >50% necrosis | ≥ 20 |
| | Grade I: ≤ 3 points. | | |
| Final score | Grade II: 4 to 5 points. | | |
| | Grade III: ≥ 6 points. | | |

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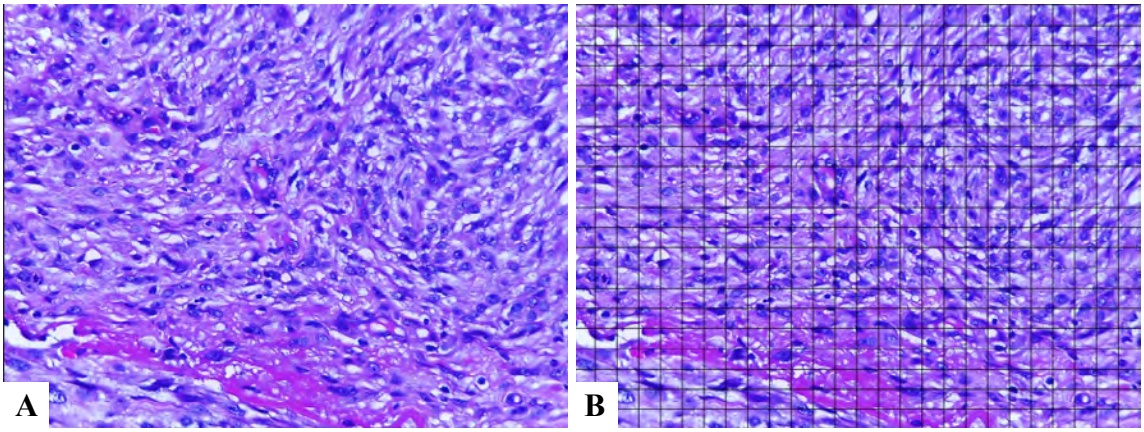


**Figure 1.** Canine soft tissue sarcoma. **A.** Histological section of a high-grade sarcoma. **B.** Same histological section superimposed with a grid with 500 dots in Microsoft Power Point 2010. HE, 40x objective.

different and random histopathological fields (40x). (Fig. 1A). Each image was superimposed with a grid with 500 dots in Microsoft Power Point 2010 (Fig. 1B). The dots that focused on cytoplasm or stroma, and nucleus, were counted, totalling 2500 dots per animal (Fig. 2). From the volumetric proportion of these components, it was possible to estimate the nucleus / cytoplasm ratio. Blood vessels (microvessels) with red blood cells were also counted in five images of each patient's tumour.

The data were analysed in a descriptive manner, characterizing the studied population and the histopathological and histomorphometric features. Inferential statistics, with a significance level of 5%, were used to compare the number of vessels and the nucleus-cytoplasm ratio, according to tumour grade and location. The data were previously submitted to the Kolmogorov-Smirnov test, to assess normality. Data with normal distribution (nucleus: cytoplasm ratio) were compared by analysis of variance (ANOVA) and Fisher's test. Data with non-normal distribution (number of vessels) were submitted to non-parametric evaluation by the Kruskall-Wallis ad-hoc Dunn's test. The Spearman test was used to assess significance and measure the correlation between clinical aspects (breed, age, tumour location, clinical staging), histopathological and histomorphometric features. Significant correlations were considered strong when $rS > 0.7$, moderate when $0.3 < rS < 0.7$ and weak when $rS < 0.3$. The disease-free interval and the survival of each patient were calculated from the date of surgery until the recurrence and death related to the disease, respectively, and these parameters were estimated using the Kaplan-Meier curve.

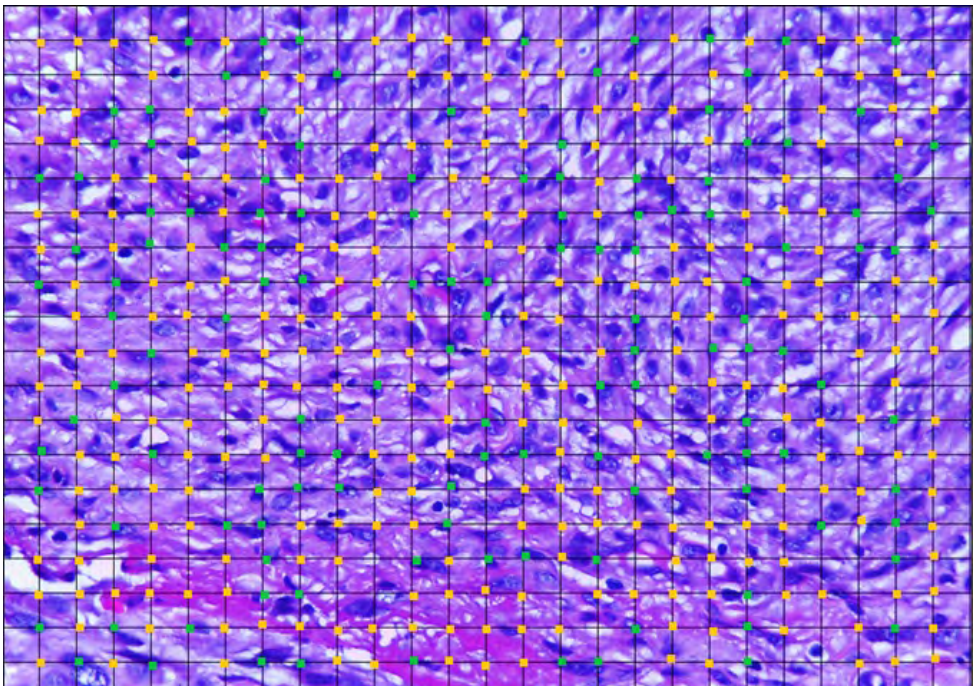

**Figure 2.** Canine soft tissue sarcoma, high grade, superimposed with a grid in Microsoft Power Point 2010, containing 500 dots focused on cytoplasm or stroma (yellow) and nucleus (green). HE. 40x high field.

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**Table 2.** Histopathological type and rating according to Trojani et al. (1984), for the 30 dogs with soft tissue sarcoma.

| Histological type | Grade (Trojani et al, 1984) | | | Total and percentage by histopathological type |
|---|---|---|---|---|
| | *I* | *II* | *III* | |
| Peripheral nerve sheath tumour | 6 | 3 | 0 | 9 (30%) |
| Angioliposarcoma | 1 | 0 | 0 | 1 (3%) |
| Fibrosarcoma | 3 | 1 | 0 | 4(13%) |
| Lymphangiosarcoma | 0 | 1 | 0 | 1 (3%) |
| Leiomyosarcoma | 1 | 2 | 1 | 4 (13%) |
| Liposarcoma | 2 | 0 | 0 | 2 (7%) |
| Myxosarcoma | 2 | 1 | 0 | 3 (10%) |
| Histiocytic sarcoma | 0 | 1 | 0 | 1 (3%) |
| Undifferentiated sarcoma | 0 | 4 | 1 | 5 (17%) |
| Total and percentage by grade | 15 (50%) | 13 (43%) | 2 (7%) | 30 (100%) |

## Results

The individual data obtained for the 30 dogs with STS used in this study are shown in supplementary data.

Of the 30 patients, 40% were of mixed breed (12/30), and the remaining dogs were distributed in the following breeds: Dachshund (2/30), French Bulldog (2/30), Belgian Shepherd (2/30), Poodle (2/30), Rottweiler (2/30), and a representative of each of the following breeds: Shih-tzu, Akita, Dogue de Bordeaux, American Pit Bull Terrier, Labrador, Lhasa Apso and Miniature Pinscher. Regarding the gender, it was observed 63% (19/30) female and 37% (11/30) male. Reproductive status was reported in 50% (15/30) of dogs, 80% (12/15) were neutered (eight females and four males), and 20% (3/15) were intact (one female and two males) – neutering occurred before STS diagnosis in nine patients, on the day of its resection in two patients, after resection in a single dog, and 20% (3/15) remained intact (one female and two males). The age of the patients ranged from two to 15 years (9.5 ± 3.4), with 63% of patients remaining in this range when diagnosed with sarcoma.

Regarding the location, 80% (24/30) of the STS were located in the subcutaneous connective tissue and 20% (6/30) in the viscera. Of the tumours diagnosed in the subcutaneous tissue, 46% (11/24) were located in one of the limbs, 21% (5/24) in the perineal region, 12.5% (3/24) in the mammary gland, and 4.1% (1/24) in the following locations: ear, cervical region, flank, dorsolumbar and one without specified localization. Of the visceral tumours 33.3% (2/6), were located in the spleen, and 16.6% in the following organs: bladder (1/6), small intestine (1/6), cecum (1/6) and uterus (1/6).

Undifferentiated sarcoma represented 17% of cases (5/30) and peripheral nerve sheath tumour represented 30% (9/30). Either fibrosarcoma (4/30) or leiomyosarcoma (4/30) represented 13% of cases. Table 2 shows the histological variants found in the study and their respective percentages (%).

In regard to tumour grade (9, 35), grade I STS were obtained in 50% of cases (15/30), and grade II or III tumours compromised 43% (13/30) and 7% (2/30) respectively. The mitotic index ranged from zero to 26 (5.8 ± 7.5).

In the histomorphometric analysis (n = 30), the nucleus:cytoplasm ratio varied from 0.01 to 0.98 (0.43 ± 0.2) but there was no significant difference according to tumour grade or location through ANOVA and Fisher test. A greater number of microvessels was observed in grade II / III STS located in the subcutaneous tissue compared to grade I, in the same location, and visceral STS (regardless of graduation) through Kruskall-Wallis test (p = 0.004) (Table 3). In spite of that correlations were positive, and increased nucleus:cytoplasm ratio was moderately associated with higher tumour grade (p = 0.05; rS = 0.361) and mitotic index (p = 0.05; rS = 0.355), while the number of microvessels

**Table 3.** Average and standard deviation for nucleus-cytoplasm ratio and number of microvessels according to ratingfollowing the schemes proposed by Trojani et al. (1984) for soft tissue sarcomas in dogs. Different lower-case letters within the same category indicate a significant difference (p <0.005).

| | Nucleus-cytoplasm ratio | | Number of microvessels | |
|---|---|---|---|---|
| | *Grade I* | Grade II/III | Grade I | Grade II/III |
| Subcutaneous (n = 24) | 0.27 ±0.1 (a) | 0.3 ± 0.08 (a) | 21.1 ±17.6 (a) | 82.4 ±0.3 (b) |
| Visceral (n = 6) | 0.3 ± 0.14 (a) | | 19.5 ± 25.7 (a) | |
| STATISTIC | ANOVA e Fisher (p = 0.6) | | Kruskall-Wallis ad-hoc Dunns (p = 0.004) | |

*Different lower-case letters within the same category indicate a significant difference (p <0.005).*

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**Table 4.** Correlation by Spearmann´s test of clinical, histopathological and morphometric data of 30 soft tissue sarcomas in dogs. *Grading performed according Trojani et al. (1984). The significant correlations (p<0.05) were considered strong when rs>0.7, moderate when 0.3<rs<0.7 and weak when rs<0.3.

| Analysis data | P | rs |
|---|---|---|
| Grade* vs. Degree of Differentiation | 0.004 | 0.508 |
| Grade* vs. Necrosis | 0.001 | 0.592 |
| Grade* vs. Mitotic index | 0.002 | 0.533 |
| Grade* vs. Nuclear pleomorphism | 0.003 | 0.52 |
| Grade* vs. Nucleus/cytoplasm ratio | 0.05 | 0.361 |
| Location vs. Mitotic index | 0.039 | 0.378 |
| Degree of differentiation vs. Nuclear pleomorphism | <0.0001 | 0.932 |
| Nucleus/cytoplasm ratio vs. Mitotic index | 0.05 | 0.355 |
| Number of microvessels vs. Degree of Differentiation | 0.05 | 0.362 |
| Number of microvessels vs. Nuclear pleomorphism | 0.036 | 0.384 |

*The significant correlations (p<0.05) were considered strong when rs>0.7, moderate when 0.3<rs<0.7 and weak when rs<0.3.*

was positively correlated with degree of differentiation (p = 0.05; rS = 0.362) and nuclear pleomorphism (p = 0.036; rS = 0.384) (Table 4). (Table 3). The significant correlations are shown in Table 4.

Regarding the surgical margins, it was possible to standardize them in 21/30 patients. Of these cases, 14.3% (3/21) resulted in free margins, 14.3% (3/21) in narrow margins and 71% (15/21) compromised or infiltrated margins.

Clinical follow-up was possible in 50% (15/30) of the cases: two were euthanized due to advanced disease and tumour recurrence (13.3%), one died in the immediate postoperative period (6.6%) and seven were euthanized or died from causes unrelated to the tumour (46.6%). However, as they have not been necropsied, we do not rule out the possibility of distant metastases, only recurrence at the tumour site is ruled out. Five animals (33.3%) remained alive, with no tumour recurrence or signs of metastasis up till this moment. Therefore, the median disease-free interval and survival were not reached (Fig. 3).

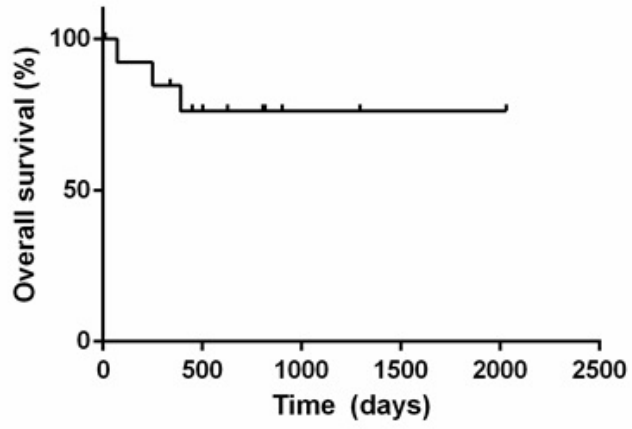


**Figure 3.** Kaplan-Meier curve showing the overall survival of 30 dogs with soft tissue sarcoma. The median was not reached.

## Discussion

STS represent the most common malignancy in insured dogs from the United Kingdon (11) and represent 8 to 15% of all cutaneous and subcutaneous tumours in dogs, although they may also occur with an unknown incidence in viscera (8, 12). Medium and large dogs are more affected, however, there is no apparent breed predisposition (4, 8, 12). Out of the 30 patients in the present study, 40% were mixed breed (12/30), and the remaining were distributed in several small, medium and large breeds. Large dogs were represented by eight animals (26.6%). The proportion of males and females is variable and does not seem to have any influence (12, 13, 22) on the development of the disease or progression, however females represented the majority of cases affected by STS (19/30; 63%).

Dogs affected by STS tend to be middle-aged or elderly. The average age of the dogs in the present study (9.5 years) was slightly lower than the average described in the literature, with an average age range between 10 and 11 years (3, 6, 9, 12, 22).

In dogs, STS occurs more frequently on the skin and subcutaneous tissue, as shown in the present study, in which 80% of the tumours (24/30) were located in the skin or subcutaneous and 20% (6/30) in the viscera. The incidence of visceral sarcomas is still undetermined, and in the present study 2/6 visceral tumours were diagnosed in the spleen, and the others in the bladder, small intestine, cecum and uterus.

Regarding the 24 dogs diagnosed with tumours in the subcutaneous region, 45% (11/24) occurred in the limbs, 4.3% in the head and 5% in the trunk region (including the tail). Subcutaneous STS were more frequent in the trunk region, which partially differs from the results found in the literature (1, 3, 12, 22) which demonstrate 60% of subcutaneous tumours in the limbs, while the trunk is involved in about 35% of the cases and the head in 5%.

 

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STS are recognized as a group of diseases with similar biological behaviour, prognosis and treatment, in humans and dogs (6, 7, 9, 10, 25, 35), without significant differences in the rates of local recurrence and metastasis according to histopathological type (25), as demonstrated in this study. Histopathological grade is the most important prognostic factor in STS in humans, and probably one of the most useful criteria for predicting outcome in dogs (2, 3, 26).

However, the distribution of STS, according to the Trojani´s grade can be influenced by the location where the studies were carried out. When performed in general care veterinary hospitals, low-grade tumours predominate (51 to 84%), and high-grade tumours are uncommon (6-3 to 7%) (3, 26). In contrast, in studies carried out at veterinary oncology reference centres, high-grade tumours are more common (22.7 to 29%), possibly due to the referral of more complex cases (17). Due to the fact that the veterinary hospital, in which the study was conducted, is a general care institution, the prevalence of the grades of tumours is befitting with the literature that showed the prevalence of STS grade I (50%), followed by grade II (43%) and grade III (7%).

High-grade STSs are associated with more aggressive biological behaviour, higher rates of local recurrence, distant metastasis and shorter disease-free intervals (9, 26). According to the analysis of the 15 patients followed, only 13.3% (2/15) presented tumour recurrence after surgical resection, values within the predicted in the literature (2, 10, 12, 17, 18, 25). Tumour recurrence increases the risk of death, related to cancer, by five times (10, 12, 18). Both tumours were classified as high grade.

Through this study, it was possible to correlate histomorphometry with the histopathological characteristics of STS, and nucleus:cytoplasm ratio was correlated with tumour grade and mitotic index, while microvessel density correlated to tumour´s degree of differentiation and nuclear pleomorphism. A greater number of microvessels was observed in grade II / III STS located in the subcutaneous tissue compared to grade I, in the same location. As sarcomas usually disseminate via haematogenous spread, greater vascularization of the tumour may be associated with a higher rate of tumour dissemination and local recurrence, since high-grade tumours demonstrate such behaviour, however further studies are necessary to validate this hypothesis.

In Veterinary Medicine, surgery represents the treatment of choice for STS (6, 8, 9, 14, 22), since these tumours have a low response to chemotherapy protocols (3, 6), and due to their behaviour, in general, little metastatic (29). The main objective is to obtain surgical margins free of neoplastic cells, which according to previous studies, is a determining factor for the disease-free interval and survival of these patients (30, 35). The qualification of surgical margins has not yet been standardized, being the subject of discussion, however, in general, wide margins or radical resection are indicated. Some authors report minimum margins of 2 to 3 cm of normal tissue around the tumour and a deep clean facial plane (10, 12, 19, 22), others recommend a more aggressive approach, indicating tumour resection up to 5 cm at the around it and up to two tissue planes deep (3, 5, 18). In the present study, the low correlation between compromised margins and recurrence can be justified by studies that point to less aggressive surgeries applied in STS, especially in tumours of low and / or intermediate grade. This is particularly true in very elderly animals, considering that the STS are located mainly in the limbs, requiring amputation to obtain free margins, since tumour recurrence may take a long period of time, sometimes exceeding life expectancy of the animal (1, 2, 20, 23). In addition, the use of local adjuvant therapies, such as radiotherapy (4, 8, 15, 16) and electrochemotherapy (24, 28, 29, 32, 33, 34), and systemic therapies, such as metronomic chemotherapy (4, 13, 29), can increase the disease-free interval.

In the present study, the median disease free-interval and overall survival were not reached in the dog population (n = 15), according to the Kaplan-Meier curve. In cases of grade I STS, by the grading of Trojani et al. (1984), obtaining surgical margins free of neoplastic cells, after removal of the tumour, is a key factor to increase survival (8). Radiotherapy is often recommended for STS, but it was not available at the time and place of this study. Inoperable tumours can be submitted to neoadjuvant radiotherapy (4, 8, 35), however, as a single therapeutic protocol, radiotherapy is inefficient in controlling or reducing STS. In a study carried out in the USA, 34 dogs with STS underwent surgical excision of the tumour and then received radiotherapy treatment (16). From the Kaplan-Meier curve, it was shown that dogs diagnosed with STS grades I and II had a median four-year survival, while those with grade III tumours had a 3.4-year survival (16). The results of this study showed that radiotherapy, used as an adjuvant therapy, is a good therapeutic option even in grade III STS.

The use of chemotherapy protocols in the treatment of STS is still controversial due to the lack of evidence. The results of two large studies have shown no response or, at best, a small benefit, with delay in local recurrence and metastasis (27), however, its use is recommended in grade III sarcomas or in the presence of metastatic disease (6, 12, 29).

The efficacy of cyclophosphamide, in metronomic dose, associated with piroxicam, was evaluated in dogs with STS with incomplete excision. The 85 dogs in this study were divided into two groups: 30 patients received metronomic chemotherapy through the association of cyclophosphamide (10mg / m²) and piroxicam (0.3mg / kg) and 55 did not receive any chemotherapy. The disease-free interval was significantly longer in animals that received metronomic chemotherapy (410 days) when compared to the control group (211 days, $P<0.0001$), suggesting that this therapeutic modality may be a viable option and with good results in local control (13).

Limitations of this study include the relatively small sample and immunohistochemistry studies not performed. However, it is largely known that the impact of grading is far superior to the impact of the histopathological subtype of canine STS.

With this study it was observed that histomorphometry proved to be useful in the evaluation of STS, representing an additional tool correlating with well-established prognostic factors (histopathological grade, nuclear pleomorphism), however, further studies, with larger samples, are necessary to validate this technique.

**Conflict of interest Statement**

The authors declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

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