Skin and Subcutaneous Soft Tissue Tumors – Feline

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Introduction

Soft tissue tumors (STTs), also referred to as soft tissue sarcomas (STS), are a group of commonly diagnosed tumors in domestic cats.[17,18,20,26,29] The recent publication from the Davis Thompson DVM foundation[32] uses the terminology "soft tissue tumors"; soft tissues for the purposes of that publication are defined as "extra-skeletal connective tissues of the dermis, subcutis and fascia, striated and smooth muscle, vessels, serosal and synovial linings and nerve sheaths."

Until recently, there was a lack of species-specific grading systems for these tumors. Previous studies have applied the human/canine STS/STT grading system[22,28,38] to feline injection site sarcomas (FISS)[9,13,31] but did not find any significant correlation between the histologic grade and outcomes. Another grading system applied to FISS also found no statistically significant correlation between grade and recurrence[19] whilst another study found that histologic grade (as described by Kuntz et al.[22]) was associated with distant metastasis.[33] Other than these FISS studies and a more recent publication proposing a novel grading system for feline STS/STTs,[12] there is one other study looking at prognostication at a particular subtype of feline STS/STT, specifically nerve sheath tumors.[34]

The existence of FISS (historically known as feline vaccine-associated fibrosarcoma), does complicate the picture for cats; these are tumors that arise at previous sites of

vaccination or other forms of localized trauma, which induce chronic inflammation.[10,14,23,27] One issue when considering grading of STS/STT in cats is whether FISS should be included within the STS/STT group or whether it should be addressed as a separate entity; if so, we need to reach a consensus on how we diagnose FISS with certainty. At this point in time, due to an absence of definitive diagnostic criteria, FISS is included within the STS/STT category for the purposes of this document, as the protocol described here is designed to help investigators to collect as complete a dataset as possible. One future goal should be to establish clear criteria to diagnose FISS specifically, and these criteria can then be applied to cohorts of tumors in future studies, both subtyped and not subtyped, to determine whether future grading systems should be specific to FISS and non-FISS tumors and also whether additional subtyping helps to achieve a more accurate prognosis.

We encourage future investigations to evaluate the prognostic utility of assessing specific tumor types separately (if the tumor type can be identified) to determine if the specific histological diagnosis is predictive of tumor behavior(s). Additional statistical evaluation of the entire group of STS/STT can be compared to that of individual tumor types to determine if histological diagnosis has a disproportionate effect on outcome that outweighs general grading criteria applicable to any STS/STT. In human medicine, the diagnosis of STS/STT is based on immunohistochemistry (IHC) findings, but there are currently no standardised IHC panels for diagnosing and subtyping feline STS/STT and this is another area of future research to consider.

The VCGP grading guidelines state that grading systems should be developed for one tumor type in one species. Grouping tumors for the purposes of developing grading systems is not ideal, but in cases where tumor types are hard to distinguish from each other, they have historically been grouped, i.e., canine STS/STTs. As soft tissue sarcomas are rare in humans, accounting for 1% of all adult malignancies with at least 100 different subtypes,[15] soft tissue sarcomas are generally graded as a group; however, an attempt to account for histologic types and subtypes is a component of these grading systems,[8,38] and there is increasing recognition for the need of subtype-specific grading systems given the heterogeneity of tumor biology.[16]

The published grading system[12] is a proposed system only, and as such there is now an urgent need for larger scale, preferably prospective, cross-institutional studies to validate and hopefully improve the system, based on a larger number of cases with comprehensive outcome data. There is also a need to assess additional individual parameters which may in future prove to have prognostic value in their own right, or as part of an alternative grading system, and a need to validate grading systems for each specific tumor subtype.

This protocol is intended for use with the following types of tumors: perivascular wall tumor (PWT), malignant nerve sheath tumor (MNST), fibrosarcoma, myxosarcoma, leiomyosarcoma, liposarcoma, or unclassified spindle cell sarcoma arising in the dermis or subcutis. The intent is to provide consistent data by standardising reporting of these tumors, including those which may be difficult to definitively diagnose as a specific subtype. It is noted that FISS may present as a variety of histological subtypes including extraskeletal osteosarcoma and extraskeletal

chondrosarcoma; these are included within this protocol, assuming their origin can be proven beyond reasonable doubt.

A goal of future investigations should be to clarify the various issues surrounding these tumors, including whether feline STS/STTs should be subtyped prior to grading, and whether FISS have their own defined set of diagnostic parameters, and their own grading system. If so, should the remaining non-FISS tumors within the feline STS/STT group be subtyped; is there prognostic information to be gained from this? Answering these questions can only be accomplished if investigators establish clear, unambiguous criterion for diagnosis and then subtype each tumor. Future studies should then compare grading systems based on grouping all feline STS/STT together versus subtyped tumors. One problem with the present canine STS/STT system is we do not know if there is any value in subtyping, and to prevent this error in future studies for both feline and canine STS/STT will require accurate diagnoses correlated with accurate outcome assessments.

Subtyping and assessment of multiple parameters, not just histological grading, may have important prognostic value. For example, one study[7] looked at prognostic factors for canine cutaneous PWTs as a distinct subtype. Ulcerated PWTs and those located on the distal extremities had a higher hazard of local recurrence both in univariate and multivariate analysis. Histological grade, necrosis, mitotic count, and infiltrated margins were all associated with local recurrence both in univariate and multivariate analysis. Boxer breed, older age, ulceration, grade III, necrosis >50% and higher mitotic count were correlated with shorter overall survival time, although breed and age lost their significance in multivariate analysis. Therefore, the prognostication of surgically excised PWTs should be based on both clinical and histopathological variables and care should be taken to ensure independence of these variables.

We recommend that histological diagnoses are based on the most recent publication from the Davis Thompson DVM foundation, "Surgical Pathology of Tumors of Domestic Animals, Volume 3: Tumors of Soft Tissue".[32]

Future studies also need to evaluate a greater number of parameters than the present histological features used. Canine studies accepted the three parameters chosen for human tumors (MC, necrosis differentiation)[22,28] yet in the original study by Trojani *et al*.[38] there were four additional parameters (cellularity, nuclear atypia, malignant giant cells, vascular emboli) these may have been predictive for canine (or feline) tumors but were not evaluated. Furthermore, grading criteria should be readily available and reproducible so other studies can replicate and validate.

We intend this protocol to guide reviewers in assessing manuscripts for publication to ensure authors have included all required data. Investigators can also use this protocol as a checklist to ensure complete data sets are included for study participants. The purpose of this protocol is to provide standards for accruing data so that, over time, large data sets with comparable information can be evaluated to enable meaningful conclusions and accurate prognostic information. This protocol is a "living" document which will be modified as new information becomes available.

Parameters to be included in feline STT/STS reports:

Histological Type (Note A)

_____ **Nerve sheath tumor (NST)**

_____ **Fibrosarcoma**

_____ **Myxosarcoma**

_____ **Leiomyosarcoma**

_____ **Liposarcoma**

_____ **Perivascular wall tumor (PWT)**

_____ **FISS (Note B) - specify histologic type _____**

_____ **Other (indicate)**

_____ **Undetermined**

Surgical Procedure

_____ **Incisional biopsy (Note C)**

_____ **Wedge**

_____ **Needle core**

_____ **Punch**

_____ **Excisional biopsy (Note C)**

_____ **Wide excision**

_____ **Amputation or hemipelvectomy**

_____ **Primary re-excisional biopsy (Note D)**

_____ **Second (or subsequent) re-excision (include number of attempts at definitive-intent resections)**

Any neoadjuvant treatment:

_____ **Neoadjuvant radiotherapy**

_____ **Neoadjuvant chemotherapy**

_____ **Radiotherapy / chemotherapy protocol (dose, drugs)**

_____ **Time between radiotherapy / chemotherapy and biopsy**

Mode of Tissue Assessment

_____ **Manual light microscopy evaluation of glass slides**

_____ **Whole slide digital image assessment**

Tumor Site Within Skin or Subcutis

_____ **Extremities (indicate site)**

- _____ **Forelimb distal to elbow**
- _____ **Forelimb proximal to elbow**
- _____ **Hind limb distal to hock**
- _____ **Hind limb proximal to hock**
- _____ **Origin from nerve or nerve root**

_____ **Over / between scapulae**

_____ **Tail**

_____ **Trunk (indicate site)** _____

_____ **Other (indicate site)** _____

Tumor Size: (Indicate if gross and/ or histologic assessment); for gross measurements, post-fixation assessment is preferred over pre-fixation;[31] MRI / CT also ideal.

Greatest dimension: _____

Additional dimensions: _____

Number of histological sections examined, and trimming method used:

_____

Presence of ulceration: _____

Deepest Tissue Layer Infiltrated:

_____ **Dermis**

_____ **Subcutis**

_____ **Fascial Planes (describe)**

_____ **Muscular layer**

_____ **Other**

Technique of assessment

_____ **Histological assessment**

_____ **Diagnostic imaging studies, method utilised** _____

(CT or MRI scan with measurements is preferred imaging technique to estimate depth of invasion)

Degree of invasive growth as assessed clinically or via imaging (imaging modality used; e.g. immobile, attached to deeper structures, semi-mobile, freely mobile?)

_____

Other Diagnostic Tools

_____ **IHC (Note E)**

_____ **Molecular (Note F)**

_____ **Digital image analysis**

Mitotic Count (per 2.37 mm^2; See VCGP Guidelines Mitotic Count and Morphologies of Mitotic Figures)

Record number of mitotic figures counted per 2.37 mm^2;on the appropriate line.

_____ **0 - 9**

_____ **10 - 19**

_____ **> 19**

Necrosis (estimated percentage of the tumor that is necrotic; See VCGP Guideline Tumor Necrosis, Note G)

_____ **0 - 10%**

_____ **11 - 50%**

_____ **> 50%**

_____ **Necrosis estimated by microscopic assessment only**

_____ **Necrosis estimated by digital image analysis**

_____ **Necrosis estimated by gross and microscopic assessment**

_____ **Necrosis estimated by imaging, method utilised** _____

Inflammation Score (Note H)

Assess the tumor for the presence and degree of inflammation. This is a subjective criterion and a recognized issue with the proposed grading system; consult with Note H(see future considerations).

_____ **None, minimal**

_____ **Mild to moderate**

_____ **Severe**

Other histological features present

_____ **Presence of material suggestive of vaccine adjuvant**

_____ **Presence of multinucleated giant cells**

(neoplastic cells containing three or more nuclei)

Margins (See VCGP Guideline Margin Evaluation)

Histologic tumor-free distance (HTFD) is the shortest distance between the tumor and the inked margin. Measure margins in millimeters as accurately as possible, rounded to the nearest mm. Consider reporting as focal if only a few foci of tumor cells are present at the margin or diffuse if large numbers of tumor cells are at the margin. (Note I; Guideline Margin Evaluation). Indicate if imaging or other technology was used to determine tumor infiltration of surrounding tissues. Consider additional, tangential margin assessment in large / invasive masses (please refer to the VCGP Guidelines Margin Evaluation for further information).

Method of margin assessment

Please select and specify all that apply:

_____ **Radial**

_____ **Tangential**

_____ **Tumor bed**

_____ Number of sections examined

_____ Parallel (bread loaf)

_____ Width between sections

_____ Number of sections examined

Were margins inked at the time of surgery?

_____ Yes

_____ No

If no, were margins inked by lab personnel?

_____ Yes

_____ No

_____ Margins not assessed (Explain)

_____ No tumor at margin; HTFD

_____ Tumor extends to margin(s); lateral / deep

_____ Focal

_____ Diffuse

Tissue types forming closest margin _____

_____ Fascial plane below tumor?

_____ Tangential

(since HTFD cannot be assessed in tangentially sectioned margins), indicate:

_____ Tumor cells present in marginal section(s)

_____ Number of sections with tumor cells

_____ Tumor cells not present in marginal sections

Lymphovascular Invasion (See VCGP Guideline Lymphovascular Invasion)

Lymphovascular Invasion (LVI; report format below)

_____ Not identified

_____ Equivocal

_____ Present

Criteria used to determine LVI

_____Thrombus adherent to intravascular tumor

_____ Tumor cells invading through a vessel wall and endothelium

_____ Neoplastic cells within a space lined by lymphatic or blood vascular endothelium

_____ Neoplastic cells in a structure that has been confirmed to be a lymphatic or blood vessel using immunohistochemistry

Number of foci of LVI within all sections examined

_____ Few (< 5 foci)

_____ Moderate (5 – 10 foci)

_____ Many (> 10 foci)

Type of vessels invaded

_____ Muscular wall evident

_____ No muscular wall evident

Site of LVI

_____ Intratumoral (number of LVI foci)

_____ Peritumoral (number of LVI foci)

Metastasis (Note J)

_____ Not present

_____Present

_____Confirmed present via:

_____Histology

_____Cytology

_____ Suspected present (Note J) via:

_____clinical assessment

_____imaging (specify mode of imaging)

If present (indicate sites):

_____ Lymph nodes (Indicate sites)

_____ Lungs

_____ Other (Indicate)

_____ Not determined

Recurrence (Note J)

_____ Not present

_____Present

_____Confirmed present via:

_____Histology

_____Cytology

_____ Suspected present (Note J) via:

_____clinical assessment

_____imaging (specify mode of imaging)

Grade[12]

_____ 1

_____ 2

_____ 3

For Outcome and Follow-up - see VCGP Guideline Outcome Assessments

Discussion:

The terms soft tissues sarcoma and soft tissue tumor (STS/STT) are used to denote a wide range of tumor types in humans, dogs and also cats. In humans, these are relatively rare tumors, accounting for approximately 1% of all malignant tumors in the adult population.[16] For humans, there are over 100 different histological subtypes within the STS category, and this includes tumors arising most commonly on the trunk, extremities, but also in the retroperitoneal space. The most frequently diagnosed include liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS). As per the 2020 World Health Organisation classification of soft tissue tumors for humans, these tumors are categorised as adipocytic, fibroblastic or myofibroblastic, fibrohistiocytic, smooth muscle, pericytic, skeletal muscle, vascular, gastrointestinal stromal, nerve sheath origin, chondro-osseous, undifferentiated/unclassified or uncertain.[16]

The histological subtypes included in the STS group for human and canine patients varies, although there is overlap; there is also a difference in the prevalence of the different subtypes between humans and dogs. Thus the subgroup of STS/STT to which the grading is applied is not synonymous between the two species. For cats, there is even less data about specific histological subtypes and their relative frequencies, but the STS/STT group would include NST, fibrosarcoma, myxosarcoma, leiomyosarcoma, liposarcoma, perivascular wall tumours (PWT) and unspecified spindle cell tumours/sarcoma arising in the dermis or subcutis, regardless of their degree of differentiation.[32] Once again, there appear to be differences in the

prevalence of different subtypes between dogs and cats; for example, PWT appear to be relatively rare in cats compared to dogs.

The existence of FISS adds a further complication for cats. With regards to grading, the question arises as to whether FISS should be included within the STS/STT group or whether it should be addressed as a separate entity. FISSs have been included within the STS/STT group due to an absence of clearly defined and agreed upon diagnostic criteria; however, given their propensity for biologically aggressive behavior, this may not be optimal. Future studies need to address this further. The ideal would be a consensus regarding a set of clear diagnostic criteria to allow the diagnosis of FISS with certainty. Thereafter, it should be possible to study this subgroup of tumors both as a separate entity and as part of the wider STS/STT group with greater confidence, and hence allow for the tailoring of any grading systems more specifically to FISS and non-FISS tumors, if the data thus generated are supportive.

Currently for the purposes of studies, diagnosis, grading and prognostication, we group these tumors together due to their morphological similarities, and because it can be difficult to subtype them with confidence based on their histological features alone. A panel of immunohistological stains are often needed to diagnose a more specific subtype but this is generally not warranted in a routine diagnostic setting given the presumption of similar biological behaviors and the cost implications to clients. However, there are potential implications when we group these different tumors together for the purposes of prognostication; we are assuming that tumors of different histological subtypes will behave in a very similar biological manner, when this may not in fact be the case. For example, a study looking specifically at NSTs arising in the skin and soft tissues of cats[34] found no evidence of metastatic disease. By grouping these tumors together for study purposes, we potentially risk missing valuable information about the individual histological subtypes in terms of more specific prognostic parameters. Thus, the effect of grouping such tumors together within grading schemes needs to be compared to the effect of separating them into specific histological types. This is particularly the case for the rarer histological subtypes within the group; comparisons where some groups are very small are statistically weak, potentially leading to Type 2 statistical error.

Margin assessment is also of great importance, but there is no standard approach for methodology or reporting of margins. Radial assessment is common, but tangential margins should also be assessed in specific cases, such as FISS,[19,32] higher grade

tumors or very large tumors. For dogs and cats, local recurrence would appear to be a more frequent occurrence and more likely cause of death, even when metastatic disease is suspected, than in humans with STS; it is uncommon for it to be confirmed with biopsy and histopathological assessment in veterinary patients. The likelihood of local recurrence is at least partially dependent on the completeness of the surgical excision, but assessing the impact of this and disentangling it from any effect of the histological grade on outcome is fraught with difficulties. This is partly due to a lack of consistency when it comes to assessing surgical margins, and the terminology used, such as "close", "narrow", and "clear". Such subjective terms should be avoided in a pathology report.[21] It may be that the impact of histological grade is most notable for patients with narrow or marginal excision of the tumor[1,5,6,11,22,28,36,39] but further studies are needed to elucidate this, particularly with regards to feline STS/STT, for which currently such data is largely absent.

For this reason, standardizing the collection of data concerning margin assessment is vital for future studies. There are different methods to determine margin assessment and margin reporting, including assigning a score based upon the HTFD or the extent of tumor at the margin (M1-M4).[37] Another proposal involves scoring the extent of residual tumor with scores of RX (residual tumor could not be assessed); R0 (no residual tumor); R1 (microscopic residual tumor); R2 (macroscopic residual tumor).[2,24,40] These different systems should all be evaluated in clinical patients with outcome data to determine the optimum means for assessing margins with regards to prognostication. Future studies should attempt to determine if a HSM (histological safety margin) can be established for this tumor type in cats.

The grading scheme described by Dobromylskyj et al.[12] is only a proposed system based on a small scale retrospective study. As such, there is now a need for much larger scale, preferably prospective studies to validate it fully, ideally via multicenter collaborations and including detailed margin assessments. The subjective nature of the inflammation score is another issue, although the differentiation score it replaces in the Trojani scheme[38] used in human STS and applied to canine STS/STT[22,28] is also subjective. It would be advantageous if all criteria within any grading system were objective, readily obtainable from routinely-stained hematoxylin and eosin sections and easy to assess, thereby reducing variability between pathologists and laboratories. Further guidelines or methods for reducing the subjectivity this component of the proposed grading system are needed. Another area requiring further agreement is over which histological subtypes to include and whether FISS

should be included or not. If we decide FISS should be addressed as a separate entity, we need to reach a consensus on just how we diagnose FISS with certainty. It might also be more beneficial to establish a two tier grading system than the currently proposed three tier system; this could potentially aid clinicians when making decisions with regards to therapeutic options.

Notes:

A. **This protocol is intended to address what data should be gathered on feline STT/STS arising in the skin and subcutis, and of histological types which have previously been classified in the literature as "soft tissue sarcomas". For the purposes of this protocol, this consists of nerve sheath tumors, fibrosarcoma, myxosarcoma, leiomyosarcoma, liposarcoma, perivascular wall tumors, and unclassified / poorly differentiated spindle cell tumors / sarcomas. It is not intended for tumors arising from muscle, spinal nerves/nerve roots, cartilage or bone. Feline injection site sarcomas are included in this protocol, with the acknowledgement that they may present as a variety of different histological subtypes, including extraskeletal osteosarcoma and extraskeletal chondrosarcoma. These two histological subtypes can be included within this protocol, on the assumption that their extraskeletal origin can be proved beyond reasonable doubt. Studies should also evaluate the prognostic utility of assessing specific tumor types separately (if the tumor type can be identified) to determine if the specific histological diagnosis is predictive of tumor behavior. Additional statistical evaluation of the entire group of STT/STS can be compared to that of individual tumor types to determine if histological diagnosis has a disproportionate effect on outcome that outweighs general grading criteria applicable to any STT/STS.**

B. **Certainty of the histological diagnosis of FISS is aided by clinical information including the location of the tumor (known sites of previous injections or trauma) and histological features of the tumor including: a central necrotic or hyalinized/hypocellular area, peripheral follicular-like lymphoid aggregates, presence of adjuvant-like material in macrophages, and scattered giant multinucleated cells.**

C. **It is not usually possible to assess all parameters from incisional biopsy specimens. In dogs, one study compared pre-surgical biopsy and excisional surgical specimens in terms of grading accuracy and advised that grading determined by pre-treatment biopsy should be interpreted with caution.[30] Excisional biopsies should be the goal for inclusion in this protocol.**

D. **Primary re-excision refers to wide resection of a scar at a site at which initial tumor excision left microscopic residual disease or in which insufficient information was available to confirm completeness of the excision. If the specimen is from a re-excisional biopsy procedure, then the original diagnosis and tumor grade should be reported together with diagnosis and grade of the re-excised tumor. The significance of tumor grade of recurrent STS/STTs has not been documented.**

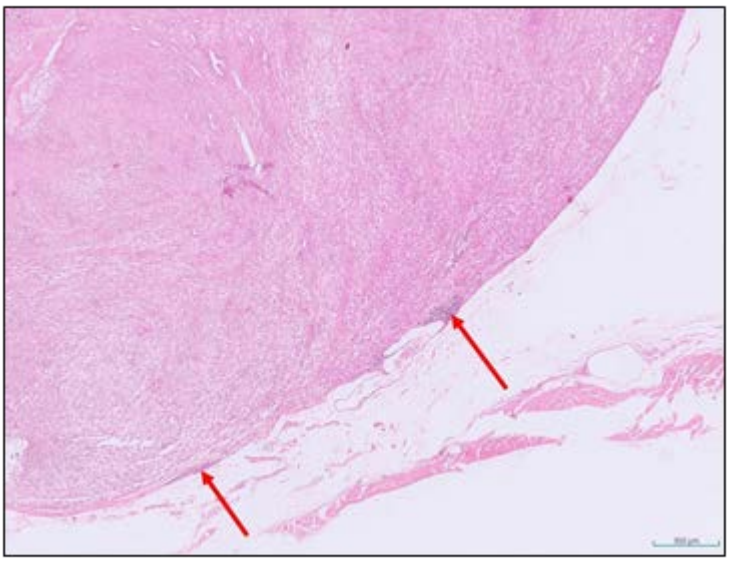
E. **There are relatively few studies describing IHC markers in feline STS/STT. More specifically for FISS, studies have assessed tumors for expression of vimentin, S100, desmin, Cox-2 and *c-kit*.[4] Studies focusing on NST have assessed tumors for expression of S100, GFAP, NSE, laminin and SMA[25,34] and one study assessed fibrosarcomas for the expression of *c-kit*.[35] If immunohistochemical studies have been performed on an individual tumor, all of the staining results, positive or negative, should be recorded, including markers which aid in the exclusion of other cells of origin that might present as spindle cell neoplasms, for example melanocytes, histiocytes and endothelial cells.**

F. **Indicate type of molecular test performed, method and results.**

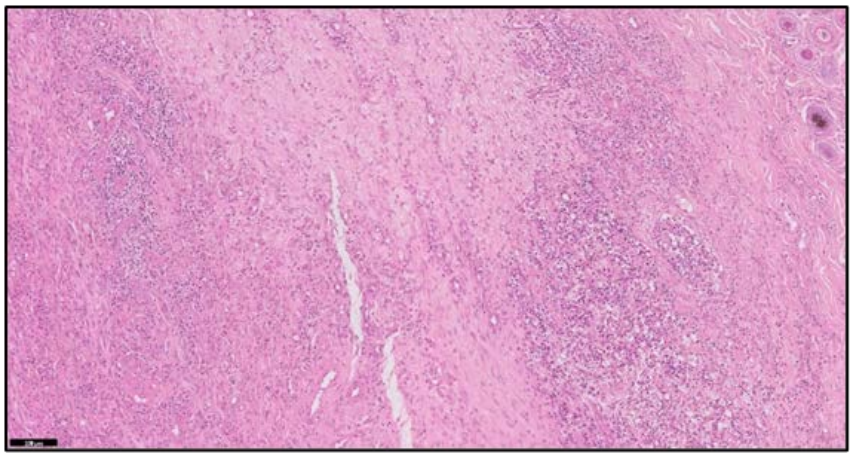
G. **The percent tumor necrosis is included in this protocol because this parameter has been utilized in published tumor grading schemes in humans and animals.[12,22,28,38] The means of assessing the percent of necrotic tumor has not been fully defined and remains subjective. Please refer to VCGP Guidelines on Tumor Necrosis. For example, investigators should state if necrosis was assessed via manual (visual)**

light microscopy with glass slide evaluation, computer assisted whole slide imaging, and whether morphometry or other objective means used to quantitate, how many sections were assessed and whether at trimming any guidance was given with regards trimming areas of necrosis.

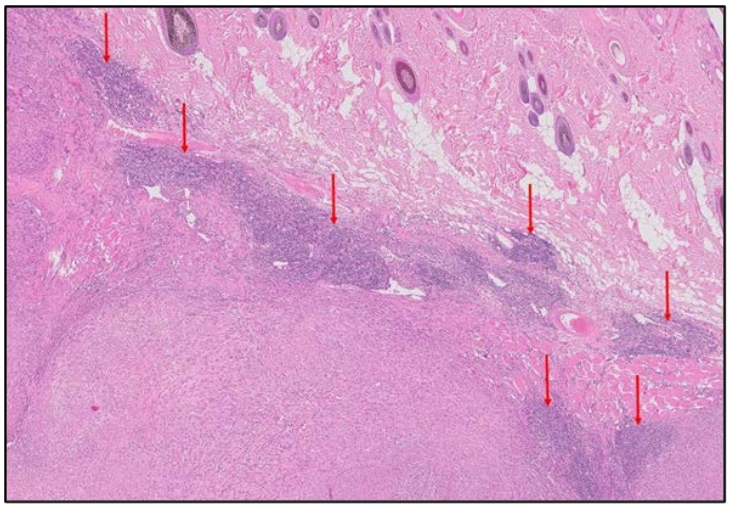
H. **The inflammation score is subjective and this is a recognized issue with the proposed grading system. Examples of a tumor which would score 1 for none, minimal or very mild inflammation may demonstrate only occasional focal lymphoid aggregates at the periphery, or low numbers of neutrophils associated with a focal area of erosion or ulceration. As guidance this may represent between 0 - 10% of the periphery of the mass as being associated with inflammatory cells. A tumor scoring 2 for mild to moderate inflammation might demonstrate focal aggregates of inflammatory cells present at the periphery in several fields, including neutrophils, macrophages, lymphocytes and plasma cells; as guidance this may represent up to 50% of the periphery of the mass being associated with inflammatory cells. A tumor scoring 3 for severe inflammation is likely to be surrounded by a nearly complete rim of mixed inflammatory cell infiltrates, with inflammatory cells also often present within the mass itself; as guidance this would likely represent more than 50% of the perimeter of the mass. Examples are shown below:**



This tumor was of intermediate histological grade (grade II) and scored 1 for none or minimal, with occasional focal lymphoid aggregates at the periphery only (red arrows).



This tumor was of intermediate grade (grade II) and scored a 2 for moderate inflammation. There were *focal* aggregates of mixed inflammatory cells present at the periphery in several fields.



This tumor was of high grade (grade III) and scored a 3 for severe inflammation. Most of the mass was surrounded by mixed inflammatory cell infiltrates, with neutrophils often present within the mass itself and associated with the areas of necrosis.

I. The histologic tumor free distance (HTFD) should be reported as accurately as possible; in mm with no decimals; report lateral and deep margins. The HTFD is the shortest distance from the tumor to the inked margin. If ink is not present when tissue is received indicate if lab personnel inked what they interpreted as deep and lateral margins. When tumor cells are seen at a margin consider indicating focal (only a few foci of tumor cells are present) or diffuse (large number of tumor cells present at the margin). There are inherent inaccuracies in margin assessment as a result of post-surgical tissue shrinkage, shifting of tissue planes following surgery, marking ink dissection along fascial planes, function of cut and formalin fixation tissue shrinkage. Alternate methods of reporting surgical margins are topics of current discussion, including a system modified from human systems designed to address breast cancer (see VCGP Guideline Margin Evaluation).

J. Metastatic sites and recurrence should ideally be confirmed by histological evaluation. Imaging results suggestive of metastasis or recurrence but not confirmed histologically should be reported as suspected metastases and mode of imaging stated: radiographs, CT, MRI etc (see VCGP Guideline Outcome Assessments). If lymph nodes are evaluated, method of evaluation should be included (e.g. FNA, incisional biopsy). A recent canine study[3] has proposed a clinicopathological staging system incorporating staging (tumor size (T), nodal involvement (N), distant metastasis (M) - TNM) together with grading. For studies acquiring data on metastasis in feline STT/STS consider a TNM type record for these cases also.

Future Consideration:

1. Validation of the proposed grading system;[12] larger scale, preferably prospective studies, ideally via multicentre collaborations and including detailed margin assessments.

2. Application of grading system to all tumor types and assessments of clinical outcomes, then assess the prognostic utility of the grading system when applied to each specific histological type of tumor within the broader category of STT/STS. Determine if the specific histologic subtype is predictive of outcome regardless of grade.

3. Address the question of whether FISS should be included within the STS/STT group or considered separately.

a. Reach a consensus regarding a set of clear diagnostic criteria to allow the diagnosis of FISS with certainty.

b. Study this subgroup of tumors both as a separate entity and as part of the wider STS/STT group and allow for the tailoring of any grading systems more specifically to FISS and non-FISS tumors, if the data thus generated is supportive.

4. Standardize the method of and collection of data concerning margin assessment; different systems should be evaluated in clinical patients with outcome data to determine the optimum means for assessing margins with regards to prognostication.

5. Establish more robust criteria for the inflammation score, so that this is more reproducible, including types of inflammatory cells, number of inflammatory cells, location of inflammation (i.e. associated with an ulcerated surface, at the periphery, associated with necrotic areas).

6. Compare new parameters to previously established/validated prognostic parameters. Assess each independently, with different thresholds. Perform univariable and multivariable analysis using all histological parameters in relation to outcome assessment.

7. Consider weighing of the individual components of the grading system

8. Consider a two tier rather than a three tier grading system, "high-risk" and "low-risk" tumours.

9. Ensure use of defined area in mm^2 for enumeration of histological features used in grading systems.

10. Develop standards for assessment of re-excision biopsy specimens should be developed and results correlated with outcome assessment.

11. Explore use of computational pathology in assessment and grading of STT/STS

12. Investigate utility of additional molecular tests in tumor grading/prognosis.

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