Feline Soft Tissue Tumors - Pathology Quick Reference Guide (PQRG) Version: FSTT Guideline 1.0 Date: January 2025

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Introduction:

Feline cutaneous and subcutaneous soft tissue tumors (STT; soft tissue sarcoma, tumors of soft tissues) are one of the most diagnosed neoplasms of the skin and subcutis in this species.[1] They have a range of clinical behaviors including infiltrative growth and variable growth rates. Local recurrence often leads to euthanasia and metastatic disease is uncommon. Tumors in this group include: fibrosarcoma, feline injection site sarcoma (FISS), nerve sheath tumor, myxosarcoma, undifferentiated sarcoma, and others.[2,3] FISS is morphologically heterogeneous; a grading system based on mitotic count (MC), necrosis and differentiation was not prognostically useful.[4]

The histologic grading system for feline STT and the prognostic features of FISS need to be validated. Until that data is published, we recommend both systems be applied to cases when a diagnosis of FISS is established and when FISS is not the diagnosis use the STT system.. When compared to other STT in cats, FISS apparently behave more aggressively (recurrence is common). Hence, when a diagnosis of FISS is established we suggest applying the “generic” feline STT grading system[2] and adding the evaluation of the two prognostic features reported for FISS: mitotic count and the major diameter measured at trimming, when the whole excised tumor is submitted.[4] Taken together, these data might help the referring veterinarian define a prognosis and identify cases with a higher risk of local recurrence.

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
- scattered giant multinucleated cells

STT Histological Grading System:

A histological grading system based on the sum of mitotic count (MC)[5], necrosis[6], and severity of inflammation was applied to 47 cats with STT in which tumors were not subtyped (there were cases of FISS within these 47 cases).[2,3]

Mitotic Count per 2.37 mm^2	Necrosis*	Inflammation**	Total Score Histological Grade
1: 0-9	0: None	1: None, minimal	δ3: Grade I Low
2: 10-19	1: 0 - <50%	2: Mild, moderate	4-5: Grade II Intermediate
3: >19	2: >50%	3: Severe	ε6 Grade III High

*Necrosis: Only histological sections were used to estimate necrosis.[2,3] There was no attempt by trimming personnel to include or exclude gross areas of necrosis.
**Inflammation: The modifiers are subjective; see images in supplementary data section for examples of each degree of severity.

Results of this study:

- **Grade correlated with median survival time (MST):** Low grade 900 days; Intermediate 514; High 283.[2,3] The total score assigned as part of grading correlated with death due to tumor-related disease (TRD).
- **MC (/2.37 mm^2) correlated with death due to TRD and MST:** median MC was significantly greater in cats that died of TRD (n=22) and their MST shorter (median MC 21, range 5-52; 205 days) than cats (n=25) that were still alive or died of non-TRD (median MC 9, range 1-70; MST 854 days).[2,3] Additional outcome data is provided in supplementary data section.
- Although necrosis and inflammation independently correlated with an outcome, we propose that these are too subjective to use as standalone parameters.

FISS Prognostic Features:

A study of 24 cases of FISS graded tumors using a sum of MC, necrosis, and *differentiation* and found that this grading system was not prognostic.[4] MC and necrosis were assessed as in the table above and differentiation scored as good (1), moderate (2), or poor (3).

Results of this study:

- **MC (/2.37 mm^2) correlated with recurrence:** MC >20/2.37mm^2 was associated with increased likelihood of recurrence (7/10 cases with MC >20 recurred). Cases had a minimum of 24 months follow-up and no deaths occurred in the NR (non-recurrent) group.
- **MC (/2.37 mm^2) correlated with euthanasia and or spontaneous death due to FISS**
- **Size correlated with recurrence:** Major diameter of formalin fixed tumor at trimming >3.75cm was associated with increased likelihood of recurrence (7/10 cases with >3.75cm diameter recurred).
- No association between completeness of surgical margins and recurrence risk.

- Recurrence was the most common reason for euthanasia; euthanasia was the most common cause of death.
- Grade, necrosis, differentiation, Ki67, margins and depth of infiltration were not prognostic. Markers associated with tumor aggressiveness (MMP-2, MMP-9, and TIMP-2) had high immunohistochemical expression, but none were useful prognostic markers.

When the histological characteristics of FISS are present, the location of the tumor is compatible and there is clinical suspicion of FISS, use the FISS Prognostic Features. We recommend also applying the STT grading system to help gather additional data. Depending on the case consider information such as the following for FISS:

Mitotic count is above/below the cutoff 20 in 2.37mm^2. A MC > 20 in 2.37mm^2 has been associated with higher risk of recurrence and death because of the tumor.

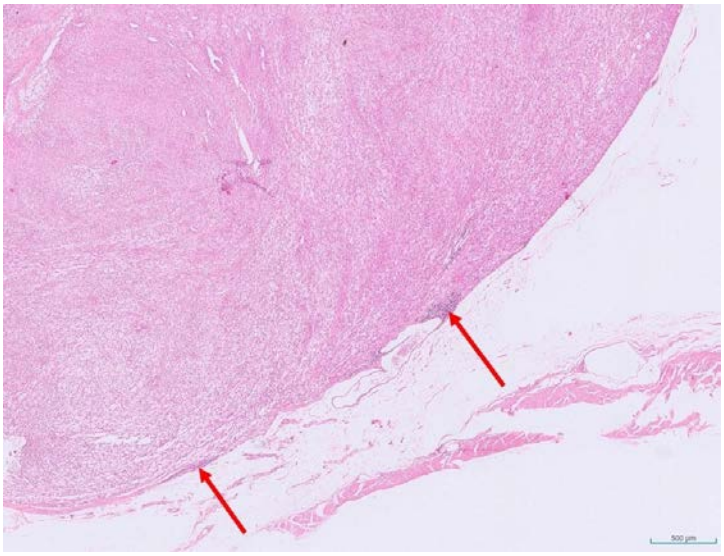
The major diameter of the tumor measured during trimming is above/below the cutoff value. A major diameter > 3.75 cm has been associated with a higher risk of recurrence and death due to the tumor.

Additional studies are needed to validate these results and should include other features such as: cytologic features of nuclei, lymphovascular invasion, infiltrative versus well-demarcated growth pattern, depth of infiltration, margin evaluation, molecular profiles of tumors and genetics of the host.[7]

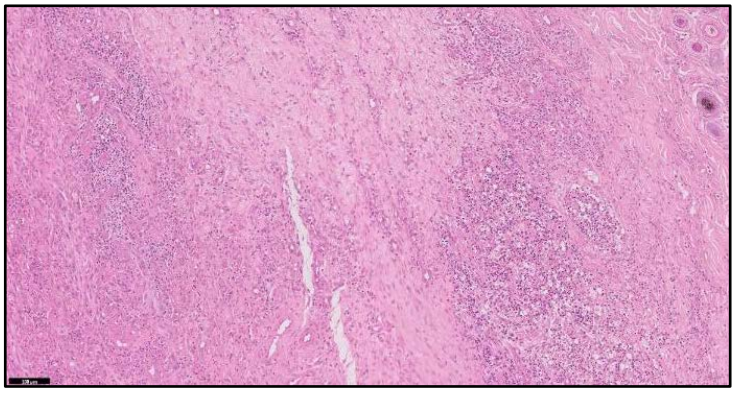
Supplementary data section - larger images of the same photos follow

Examples of inflammation severity scores:[2]

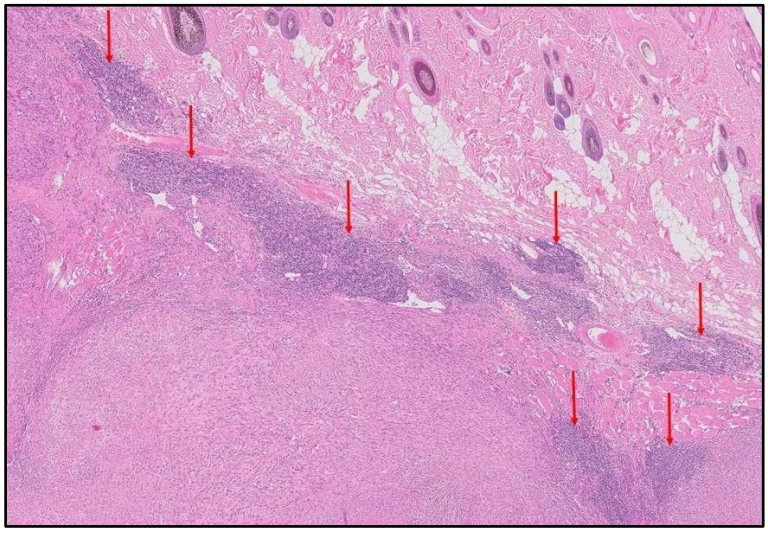
This tumor was of intermediate histological grade (grade II) and scored 1 for **none or minimal**, with occasional focal lymphoid aggregates at the periphery only (red arrows).



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.

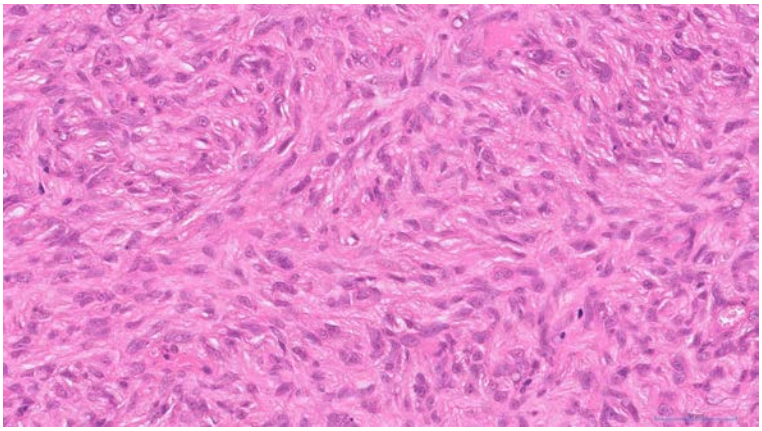


Examples of grading:[2]

This tumor was of **low grade** (grade I), with minimal inflammation (score 1), MC of 4/2.37 mm^2 (score 1) and no necrosis (score 0).

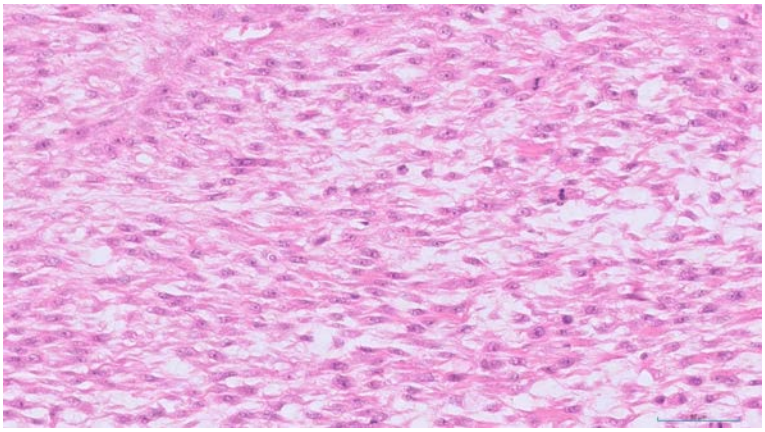
No local recurrence or evidence of metastatic disease.

Survival time – 1188 days, died of non-tumor related disease (chronic renal disease)



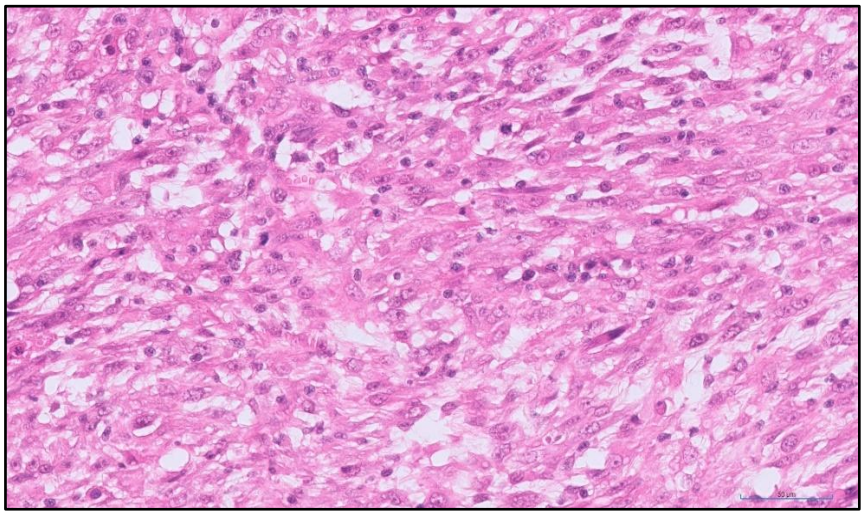
This tumor was of **intermediate grade** (grade II), with minimal inflammation (score 1), MC of 26/2.37 mm^2 (score 3) and necrosis present but less than 50% of the total tumor present in the sections overall (score 1).

This case was still alive at the end of the follow up period (1997 days later). No local recurrence.



This tumor was of **high grade** (grade III), with severe inflammation (score 3), MC of 43/2.37 mm^2 (score 3) and necrosis more than 50% of the total tumor present in the sections overall (score 2).

No local recurrence but suspected metastatic lesion in the kidney (not histologically confirmed). Survival time of 573 days.



*Note supplemental material : enlarged images at end of references

Additional outcome data:[2]
provided here from the STT Histological Grading System study (n=47):

Grade I – low grade:

- 16 cases were grade I (low grade)
- 3/16 were reported to have died of TRD during the follow up period.
    - For 2 cases treatment was not attempted
    - In the third case there was local recurrence with a survival time of 802 days
- MST for cats with grade I tumors was 900.5 days

Grade II – intermediate grade:

- 15 cases were grade II (intermediate grade)
- 8/15 were reported to have died of TRD during the follow up period.
    - 6 had reported local recurrence
    - 1 developed further masses elsewhere suspected to be metastatic disease (although histopathological confirmation was not attempted)
    - one case the reason was not reported other than 'tumor-related'
- MST for cats with grade II tumors was 514 days.

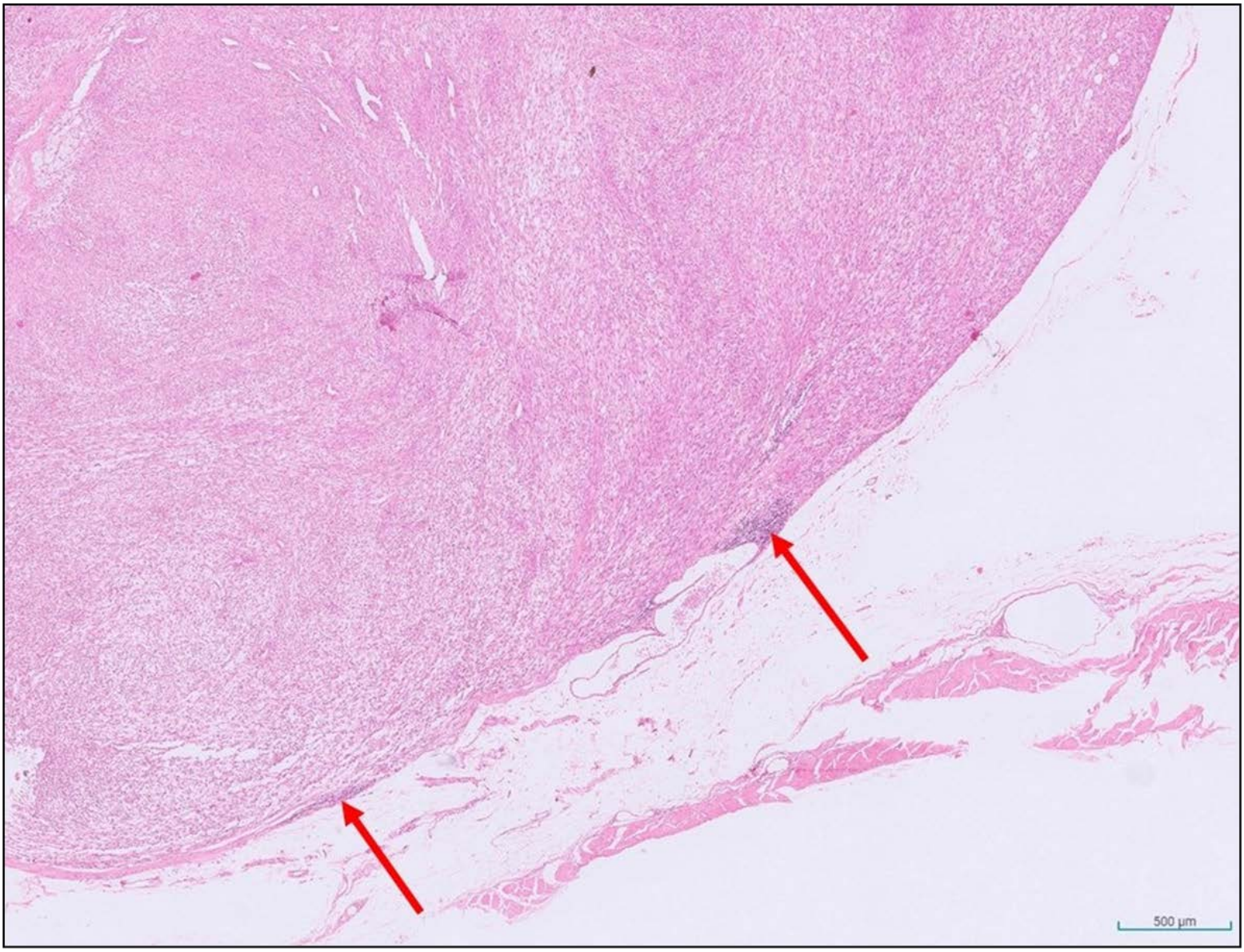
Grade III – high grade:

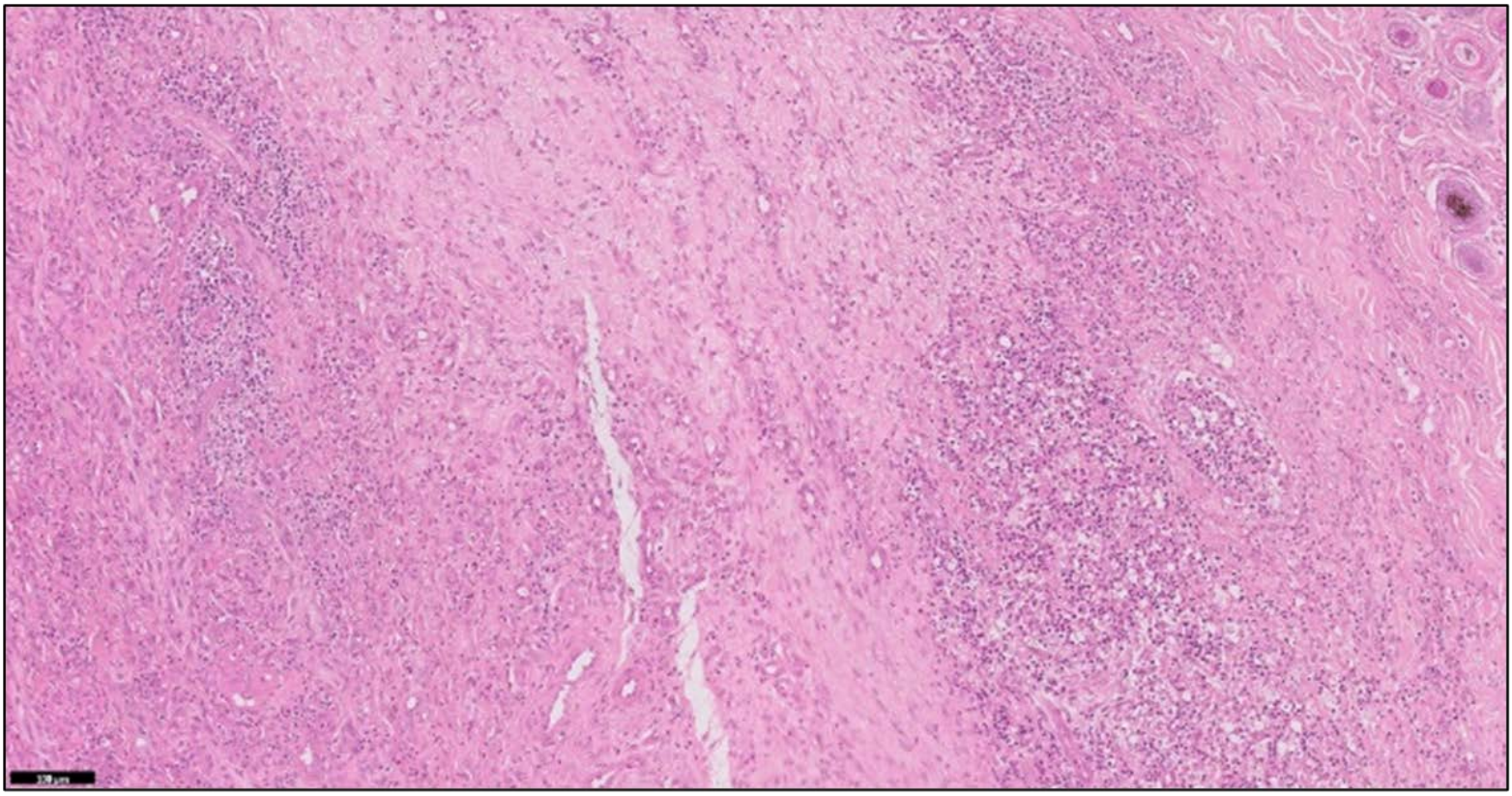
- 16 cases were grade III (high grade)
- 11/16 were reported to have died of TRD during the follow up period.
    - 4 cases had reported local recurrence
    - 4 cases treatment was not attempted
    - 3 cases developed further masses elsewhere suspected to be metastatic disease (although histopathological confirmation was not attempted).
- MST for cats with grade III tumors was 283 days.

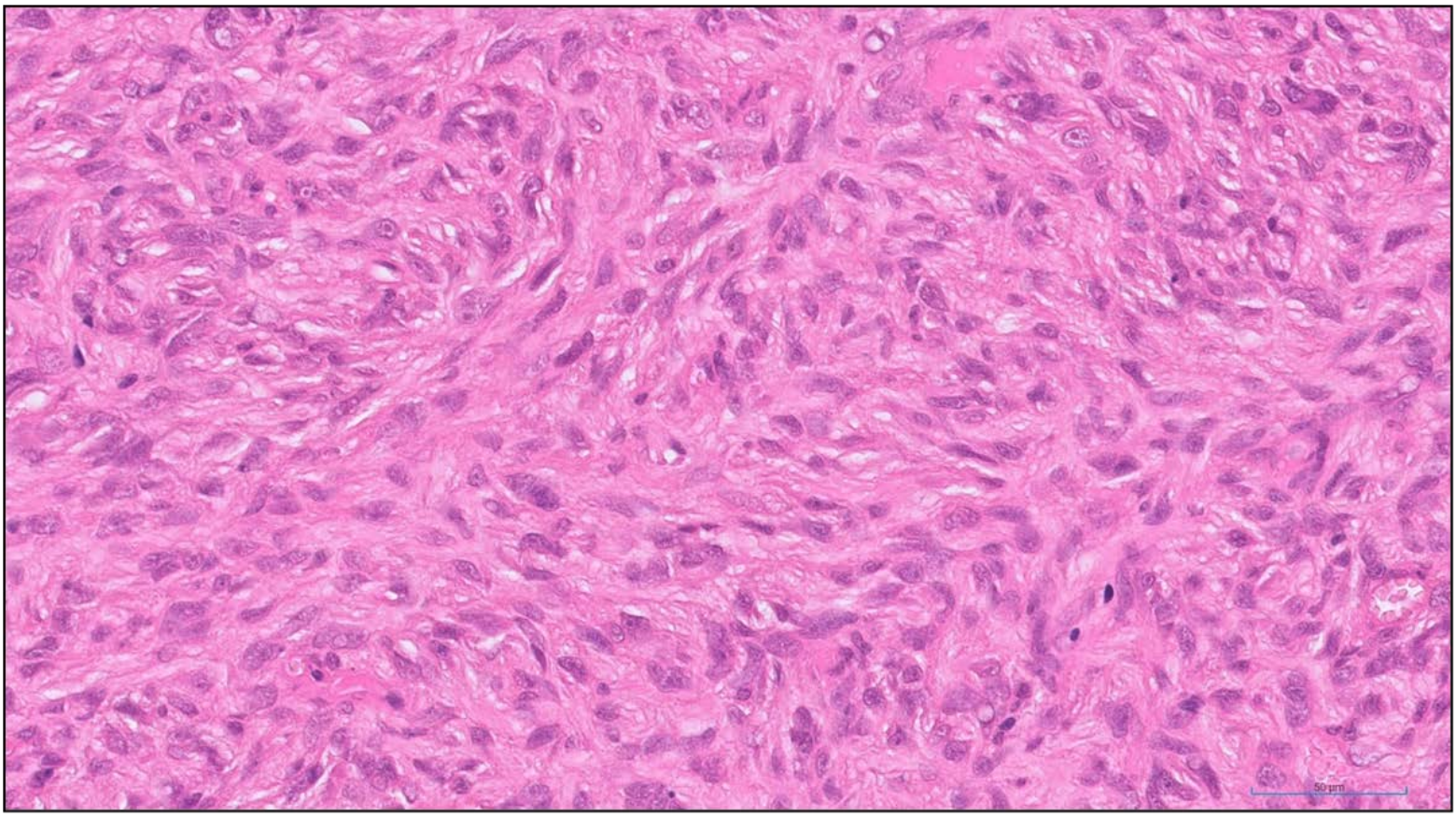
SELECTED REFERENCES:

1. Ho, N.T. et al. Retrospective study of more than 9000 feline cutaneous tumours in the UK : 2006-2013. J Feline Med Surg. 2018; 20(2) : 128-134.
2. Dobromylskyj, M.J. et al. Prognostic factors and proposed grading system for cutaneous and subcutaneous soft tissue sarcomas in cats, based on a retrospective study. J Feline Med Surg. 2021; 23(2):168-174.
3. Dobromylskyj, M.J. Feline soft tissue sarcomas: a review of the classification and histological grading, with comparison to human and canine. Animals 2022; 12(20):2736.
4. Porcellato I. et al. Feline injection-site sarcoma: matrix remodelling and prognosis. Vet Pathol 2017; 54: 204–211.
5. Meuten, D.J et al. Mitotic Count Guideline, version 1.0. Veterinary Cancer Guidelines and Protocols. http://vetcancerprotocols.org
6. Moore FM et al. Tumor Necrosis Guideline, version 1.1. Veterinary Cancer Guidelines and Protocols. http://vetcancerprotocols.org
7. Romanelli G. et al. Analysis of prognostic factors associated with injection-site sarcomas in cats: 57 cases (2001–2007). JAVMA 2008; 232: 1193–1199.

Supplementary Images: enlarged images



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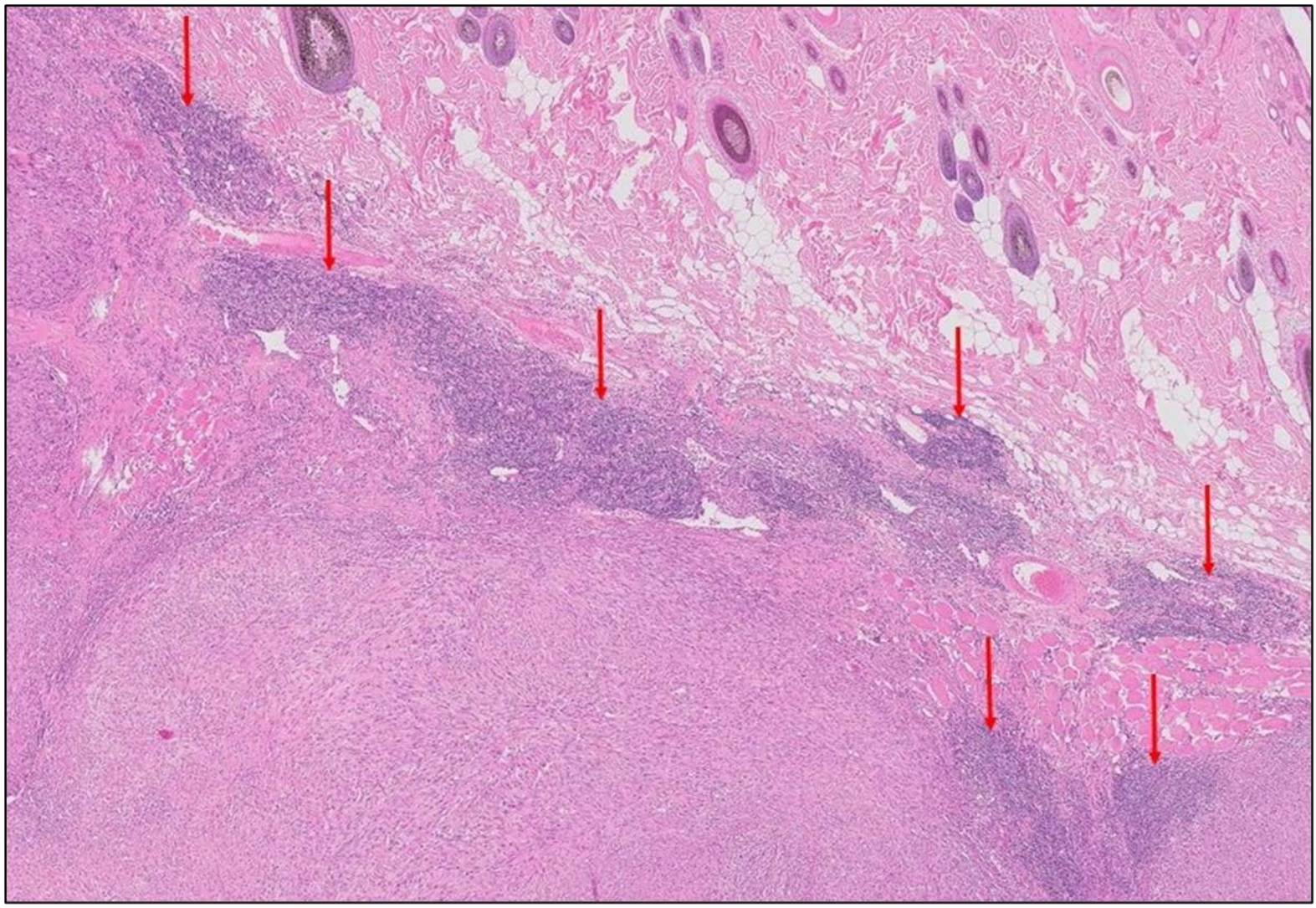

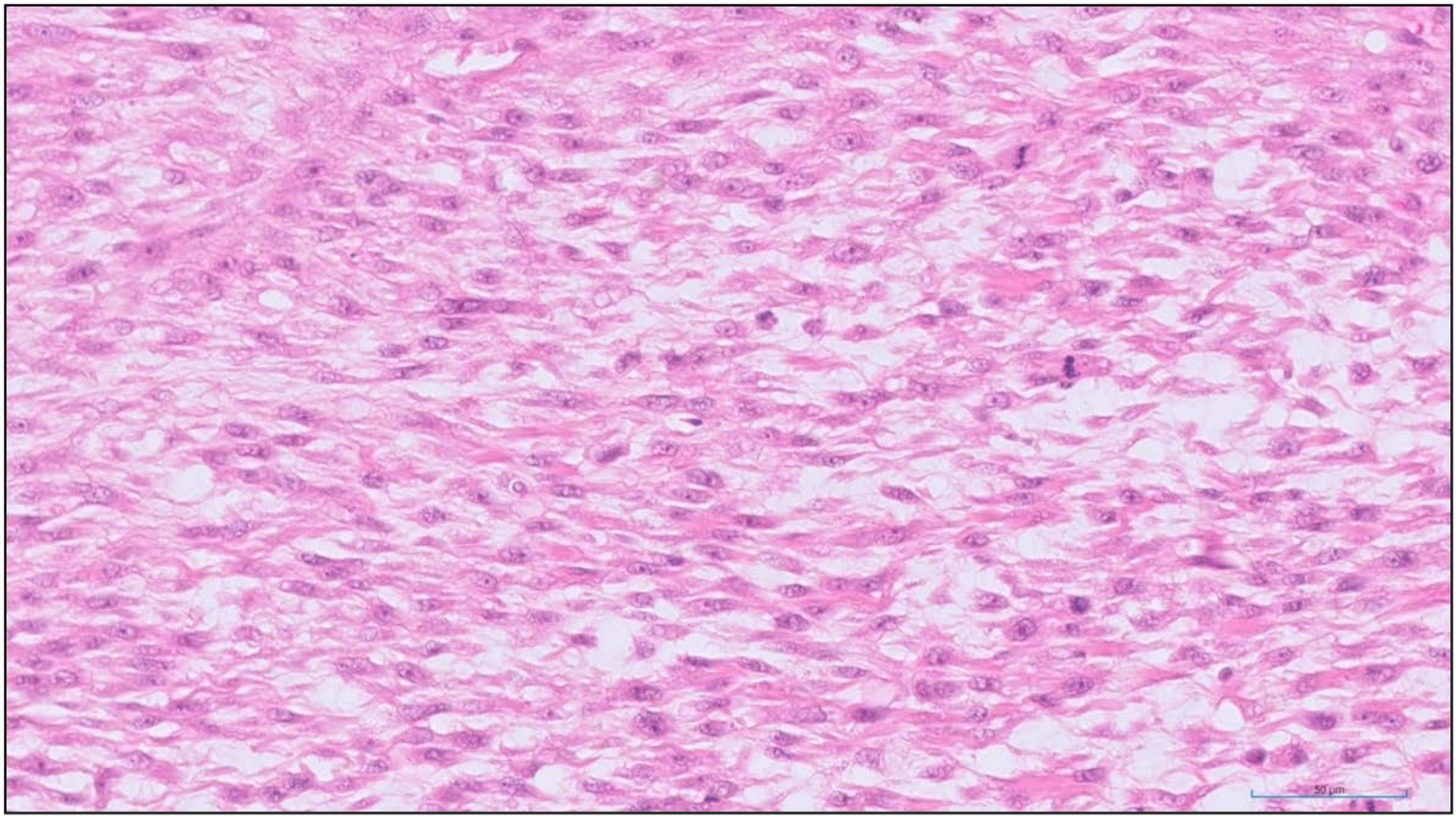
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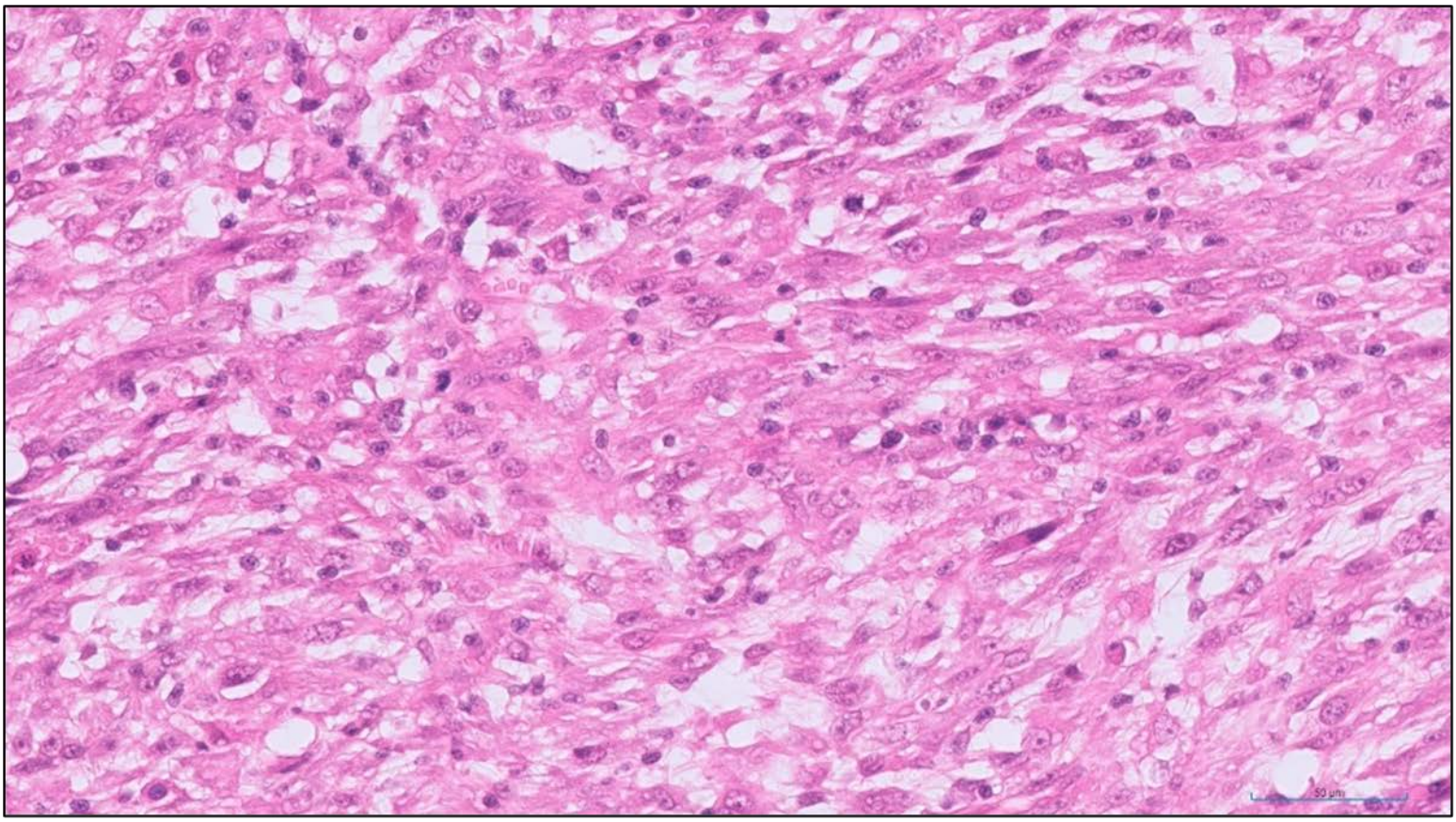
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