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ONCOLOGY

Feline Injection Site Sarcomas: Risk Factors, Diagnosis, Staging, and Treatment Algorithm

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Feline injection site sarcomas (FISSs) are malignant tumors of mesenchymal (connective tissue) origin. Conflicting epidemiologic data indicate FISSs develop as infrequently as less than 1 case per 10 000 vaccinated cats or as often as 1 in 1000 vaccinated cats.[1,2] Rabies and feline leukemia virus (FeLV) vaccines are known inciting causes of FISSs.[3] Tumors also occur secondary to injections of steroidal and nonsteroidal anti-inflammatory drugs, antibiotics, and lufenuron; microchip implantation; and inflammatory response to nonabsorbable surgical suture material.[4-8]

FISSs are highly locally invasive and differ from non–injection site sarcomas in biological behavior, including growth rate (more rapid), tissue of origin (typically subcutaneous), and metastatic potential (can be higher).[9] Injection site sarcomas also differ from non–injection site sarcomas with respect to histologic features. FISSs show increased cellular pleomorphism and mitotic activity.[9] Fibrosarcoma is the most common histologic subtype, with less common variants being malignant fibrous histiocytoma,[a] extraskeletal osteosarcoma, rhabdomyosarcoma, and chondrosarcoma.[10] High-grade FISSs show more aggressive histologic features than low-grade tumors and are more likely to metastasize.[11]

The precise etiopathogenesis of FISSs is unknown. Any stimulus inciting chronic inflammation of the subcutis can lead to neoplastic transformation of surrounding fibroblasts and myofibroblasts and subsequent

[a]The authors acknowledge that the term *malignant fibrous histiocytoma* is outdated but include it in the manuscript as it remains in the literature today. The preferred terminology used at their institution is "pleomorphic/round cell/spindle cell sarcoma with peritumoral lymphoplasmacytic inflammation (consistent with an injection site sarcoma)." *Pleomorphic* is used for less differentiated tumors with both round and spindle cell morphology.

LOCATION COUNTS
Guidelines for vaccine administration exist in order to better track association of sarcoma development with specific vaccines.

tumor formation.[3,4,10] Histologic findings include central areas of necrosis and the presence of inflammatory cells—predominantly lymphocytes and macrophages—and multinucleated giant cells. Macrophages containing aluminum and oxygen consistent with aluminum hydroxide, an adjuvant present in some feline vaccines, support the diagnosis of FISS.[10,12] A combination of an individual cat's inflammatory response and the characteristics of the injected substance contribute to development of FISSs.[10,12]

VACCINATION STRATEGIES

In 1997 the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) established specific anatomic recommendations for sites of vaccine administration.[13] This was done to better track any association of sarcoma development with a specific vaccine, as well as to potentially improve surgical control of tumors. In 2013, the American Association of Feline Practitioners Feline Vaccine Advisory Panel put forth the following instructions that vary slightly from the original guidelines:[14]

- Rabies vaccines: distal aspect of the right pelvic limb
- FeLV vaccines: distal aspect of the left pelvic limb
- All other vaccines: distal aspect of the right thoracic limb

Vaccination in these locations does not decrease the chance of tumor formation. In addition to the exact location of administration, veterinarians should document the type of vaccine, the manufacturer, and the serial number. The goal of such record keeping is for epidemiologic tracking purposes only.

Strategies to prevent or reduce the risk of FISS are controversial. Contradictory data make it difficult for practitioners to provide clear instructions to owners. The following is an outline of current suggestions, their rationale, and associated criticisms where applicable.

STRATEGY:
Administer vaccines as distally along the limb as possible.

REASON: To facilitate earlier detection and increase the likelihood of complete resection with amputation of the affected limb.

CRITICISMS:

- Cats can develop tumors along more than 1 limb. This can occur simultaneously, making amputation an ineffective option for such patients.
- Continual administration of vaccines in the distal limb increases the dose of vaccine received within a smaller anatomic area. This could lead to increased chance of tumor development as risk increases with the number of vaccines administered per site.[1]

SPECIAL CONSIDERATION: The skin overlying the flank and abdomen is mobile, giving the false impression of injecting along the limb, especially when a cat is in a "crouched" position. Ensure the vaccine is given along the limb and not in this mobile skin, as tumors along the flank and abdomen are more difficult to treat.[15]

STRATEGY:
Increase intervals between vaccinations.

REASON: To decrease overall number of vaccines over the cat's lifespan.

CRITICISMS:

- While a single dose of a commercially available inactivated, adjuvanted combination vaccine (e.g., feline panleukopenia, herpesvirus, calicivirus) provides a duration of immunity of greater than 7 years and antibodies are persistent against all 3 viruses for greater than 3 years, it is unclear whether spacing out the intervals between vaccinations decreases risk of tumor formation. However, this approach aligns with lessening the total number of vaccines administered over time, which can reduce risk.
- While rabies vaccination also provides a duration of immunity greater than 3 years, most local and/or state organizations require annual revaccination given the significant potential for zoonotic transmission of disease.

STRATEGY:
Avoid using adjuvanted vaccines.

REASON: FISSs arise from malignant transformation of fibroblasts or myofibroblasts that proliferate as part of a chronic inflammatory reaction to vaccination or injection. Adjuvants enhance immunogenicity of vaccines partially by creating inflammation.[3,4,10]

CRITICISM: The role of adjuvants in inciting inflammation and the pathogenesis of FISS is unclear. Aluminum, a common adjuvant in feline vaccinations,

was found within macrophages surrounding tumor cells.[12] However, both adjuvanted and nonadjuvanted vaccines cause inflammation. The type and severity of inflammation vary among vaccines, adjuvants, and individual patient response to vaccination.[1,10,16] It is unknown whether nonadjuvanted vaccines pose less risk of causing injection site sarcomas than adjuvanted vaccines.

STRATEGY:
Administer vaccines subcutaneously.

REASON: Tumors are more readily detected in the subcutaneous space than in an intramuscular location.

CRITICISM: No notable criticisms.

STRATEGY:
Warm vaccines to room temperature before administration.

REASON: Administration of cold vaccines was associated with a higher risk of sarcoma development than was administration of room-temperature vaccines.[4]

CRITICISM: No notable criticisms.

Type of vaccine, vaccine manufacturer, and vaccine-associated practices (such as needle gauge, syringe type, mixing of vaccines in one syringe, and multidose vaccine vials) were not associated with increased risk of tumor development.[4]

The VAFSTF recommends that vaccine protocols be tailored for each individual cat. This includes discussing the pros and cons of vaccines with cat owners. Owners need to be aware of the potential zoonotic risks, their cat's risk of exposure, any legal requirements, and the risk of development of injection site sarcoma and other adverse effects (e.g., allergic reaction). Cats developing injection site sarcomas should not receive future vaccinations. **BOX 1** lists patient risk variables veterinarians should take into consideration when designing individualized vaccination protocols.

CLINICAL SIGNS AND DIAGNOSTIC EVALUATION

Veterinarians are responsible for educating owners about the risk of tumor development. Owners can perform active surveillance for tumors by routinely touching/petting their cats. Owners should contact their veterinarian if they note a lump, especially one increasing in size or persisting beyond 1 month after vaccination. Owners are encouraged to record the location of the mass, when they first noticed it, and keep track of any changes in size. For any cat presenting with a subcutaneous mass, vaccination history is essential to identify whether a FISS is a potential differential.

Fine-needle aspiration with cytology can be helpful in ruling out diagnostic differentials, such as an abscess or other tumor. FISSs contain peripheral inflammatory cell infiltrates of macrophages and lymphocytes, which can confound a definitive diagnosis with cytology alone. The VAFSTF recommends the "3-2-1" rule for when to pursue biopsy of a suspect injection site sarcoma.[14] If a mass meets one or more of the following criteria, an incisional biopsy is recommended:

3: Mass persists for 3 months or longer

2: Mass is, or becomes, larger than 2 cm, and/or

BOX 1 Considerations When Assessing Vaccination Risk[17]

Patient variables
- Age
- Overall health status
- Risk of exposure
- Agent pathogenicity
- Geographic prevalence
- Patient history
- Chronic stress
- Aging immune response
- Maternally derived antibody interference
- Congenital or acquired immunodeficiency
- Immunosuppressive therapy
- Nutritional status

Example of YES to vaccination:
Young cat in a multicat household with outdoor access, living in an area with high prevalence of the pathogen

Example of NO to vaccination:
Geriatric cat in a single-cat household without access to the outdoors and an ineffective vaccine against a pathogen with low virulence or limited local prevalence

1: Mass continues to increase in size 1 month following an injection

If a FISS is suspected, the VAFSTF recommends an incisional biopsy be done prior to attempting surgical excision. Excisional biopsy for diagnostic purposes is strongly discouraged as tumors recur quickly and frequently when marginally excised, making future attempts at treatment challenging.[14,18] Biopsy samples are obtained from closer to the edge of the mass as the center can be necrotic. Incisional biopsy methods include needle core, punch, and wedge biopsy. Ideally, multiple samples are obtained from different locations, as tumors are often heterogeneous. Biopsy tracts must either be removed along with the tumor during a definitive surgery or included within the radiation field. Veterinarians are encouraged to discuss biopsy plans with an oncologist or surgeon.

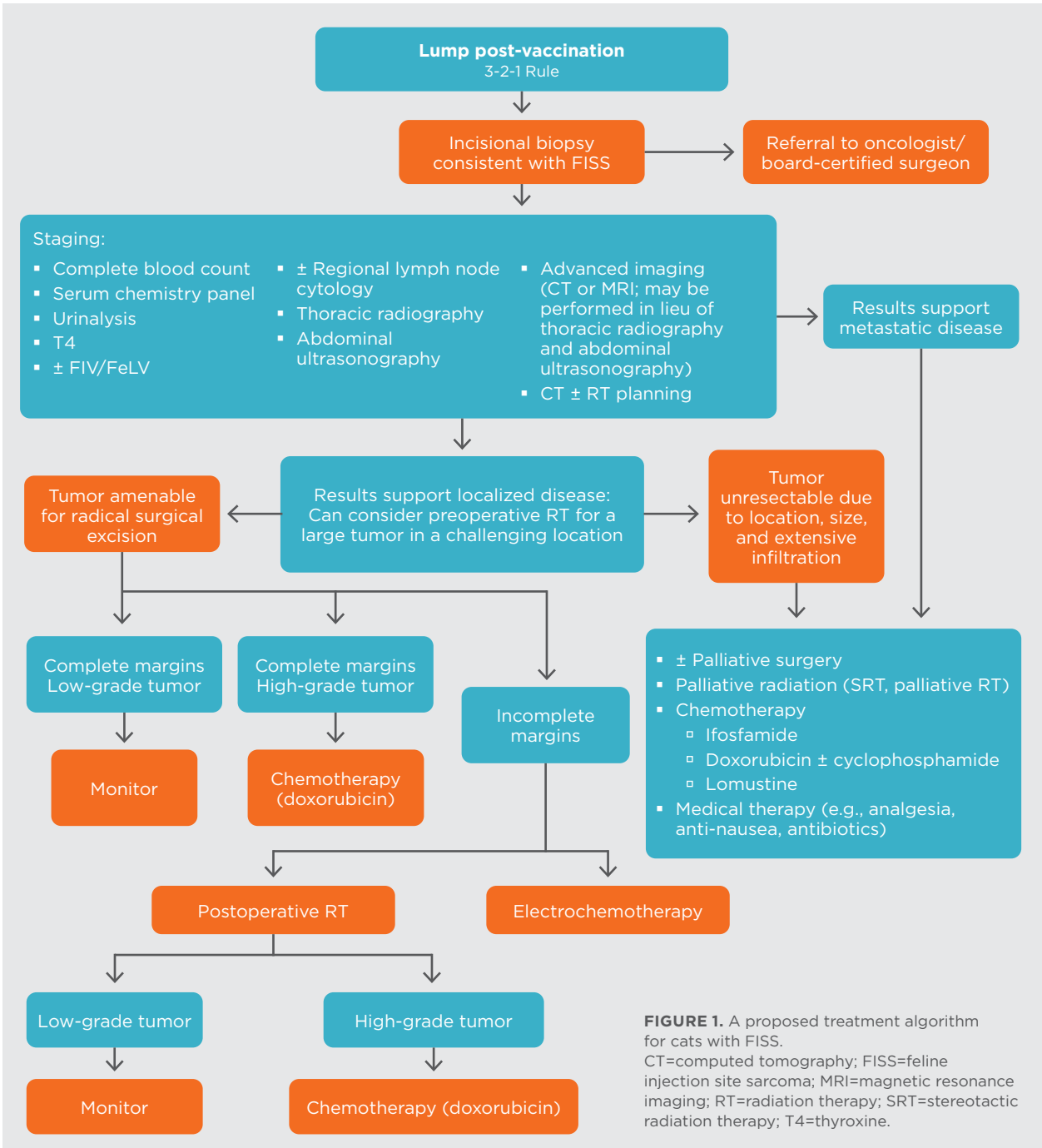

FIGURE 1. A proposed treatment algorithm for cats with FISS.
CT=computed tomography; FISS=feline injection site sarcoma; MRI=magnetic resonance imaging; RT=radiation therapy; SRT=stereotactic radiation therapy; T4=thyroxine.

General lab work (i.e., complete blood count, chemistry, thyroxine, and urinalysis) is valuable for determining a patient's overall health status prior to instituting definitive therapy. FeLV and feline immunodeficiency virus (FIV) testing can be done as part of the patient's minimum database; however, a link between FeLV or FIV infection and FISS development has not been made.[18] These tests do not provide information related to prognosis or the presence of metastasis.

Distant metastasis occurs most frequently to the lungs. Other sites include regional lymph nodes and abdominal organs.[18] Staging tests include 3-view thoracic radiography and regional lymph node examination by palpation and cytology when applicable. Abdominal imaging can be done. The authors consider computed tomography (CT) or magnetic resonance imaging (MRI) essential to an ideal treatment plan.[18] Contrast-enhanced CT scans are more accurate for determining tumor volume than physical examination estimates and caliper measurements.[19] CT scans are more sensitive than thoracic radiographs for detecting metastatic disease. Finally, with appropriate setup, CT scans can also be used for the purpose of radiation therapy planning. The high rate of local tumor recurrence, especially with incomplete margins, warrants thorough pretreatment evaluation and planning.

TREATMENT

Any sarcoma arising in the vicinity of a known injection site should be considered a FISS and treated aggressively. Treatment is challenging because tumors are locally invasive and recurrence rates approach 70%, especially in the absence of radical surgical procedures.[9] For this reason, first-line therapy for FISSs is aggressive radical surgery. Adjunctive therapies, such as pre- or postoperative radiation or chemotherapy, depend on the histologic features of the tumor, completeness of excision, and clinical status of the patient. A proposed algorithm for optimal use of treatment strategies is provided in **FIGURE 1**.

Surgery

The recommended approach includes removal of at least 5-cm margins surrounding the palpable tumor edge and up to 2 fascial planes deep, including any associated bony structures (**FIGURE 2**).[20] This approach results in complete margins in 97% of cases and a median survival time of 2.5 years. Despite radical excision, tumors recur in 14% of cases. For cats with tumors located on distal limbs or tails, wide microscopic surgical margins are possible with amputation with or without hemipelvectomy or caudectomy. Median time to first recurrence is significantly prolonged if surgery is performed by an experienced surgeon at a referral hospital compared with surgery performed at a nonreferral institution (~9 months versus ~2 months).[21] Therefore the best chance for a cat to have a good prognosis with an injection site sarcoma is a well-planned first surgery attempt.

> Excisional biopsy for diagnostic purposes is strongly discouraged as tumors recur quickly and frequently when marginally excised, making future attempts at treatment challenging.[14,18]

Not all FISSs are amenable to complete excision, defined as histologic tumor-free margins, for various reasons, including size, location, and extensive infiltration into adjacent structures (e.g., FISS arising in the interscapular region infiltrating the spine). Marginal excision alone is not recommended in such cases based on the high rate of local recurrence.

To accurately formulate a postsurgery treatment plan and prognosis, tumors must be submitted for histopathology, even when an incisional biopsy was previously done. This provides quantification of surgical margins, which predict local recurrence and survival time. Tumors with incomplete margins recur approximately 10× more frequently than those with noninfiltrated margins.[22] Cats with incompletely resected tumors had a median disease-free interval of less than 6 months versus approximately 2 years in cats with complete tumor margins.[23] Additionally, histologic subtype is significantly associated with overall survival. Cats with fibrosarcoma or nerve sheath tumors had significantly longer survival times compared with cats with malignant fibrous histiocytomas (640 days and 645 days versus 290 days, respectively).[24] Cats with higher-grade FISS are more likely to develop metastasis, which shortens survival time.[11]

Radiation Therapy

Despite aggressive surgery, recurrence rates for FISS remain high, especially when complete histologic margins are not achieved.[21] Surgery combined with radiotherapy, either pre- or postoperatively, reduces recurrence rates and extends survival compared with surgery alone in some cases. Whether to choose pre- or postoperative radiation therapy depends on tumor size, location, and feasibility of radical resection.

Preoperative external beam radiation is administered in multiple daily fractions over several weeks. The entire tumor plus 3 to 5 cm of surrounding healthy tissue is treated. Surgical excision is performed 2 to 4 weeks after completion of the radiation protocol. If the tumor can be excised completely, preoperative radiation improves time to local recurrence, metastasis, and death compared with cats with incomplete margins.[25] The pros of preoperative radiation include an overall smaller radiation field and the potential for a more conservative

FIGURE 2. (A) Injection site sarcoma located along the craniolateral aspect of the pelvic limb. Palpable tumor margins are outlined with a solid blue line. **(B)** Same tumor with 5-cm margin of skin surrounding the palpable mass marked with a dashed blue line. **(C)** Same tumor with margin extended to incorporate entire planned area of skin to be removed with amputation of the affected limb. **(D)** Intraoperative view of defect created by removal of tumor plus radical margins. **(E)** Patient immediately after surgery. In all images cranial is to the left, caudal is to the right, and dorsal is toward the top.

Courtesy Marine Traverson, DVM, MS, DACVS (5)

resection/"downstaging" of the tumor (e.g., reduction in size with treatment). The main con to preoperative radiation therapy is the delay in time to definitive surgery. Tumors can grow and/or metastasize during that interval.

Postoperative radiation is also given over several weeks and delivered to the entire surgical scar plus 3 to 5 cm of surrounding healthy tissues. Postoperative radiation therapy begins once the surgery site is healed, typically within 10 to 14 days. In some cases, a higher total dose of radiation can be administered postoperatively compared with preoperatively. This could lead to improved long-term tumor control. With postoperative radiation there is no delay to excision, histologic grade and tumor type are confirmed before committing to an intensive radiation treatment plan, and, in one study, cats had significantly longer survival times than preoperative radiation (~2 years versus 10 months). The authors in this study caution the results could be linked to case selection bias and must be interpreted carefully.[26]

There are several cons to postoperative radiation therapy, including the potential for delay in treatment due to complications related to surgical healing, which can negatively influence both the disease-free interval and survival time.[27] Another drawback to postoperative radiation is the need for a larger treatment field. This increases the potential for acute and late side effects, as a larger area of healthy tissue is affected. Brachytherapy with iridium-192 interstitial implants as an alternative form of postoperative radiation therapy was well tolerated and is comparable to other forms of therapy.[28]

Palliative radiation therapy entails fewer treatments than pre- or postoperative treatment. The goal of palliation is to reduce or stabilize tumor size and increase patient comfort. It is not expected to improve longevity. Cats with measurable tumors treated with palliative-intent radiation therapy had a progression-free interval of 4 months and a median survival time of 7 months.[29] Stereotactic body radiation therapy (SBRT) delivers high doses of ionizing radiation in a limited number of sessions (1 to 5). SBRT in 11 cats with FISS led to a complete response in 3 cats and partial response in 5 cats. The median progression-free interval was 8 months, and the median overall survival time was 10 months. SBRT may be useful for downstaging tumors prior to surgical resection.[30]

The short-term and long-term side effects of radiotherapy can be associated with significant morbidities. Short-term effects appear during treatment and persist for a few weeks after completion. Common short-term effects include dermatologic changes (e.g., skin erythema and ulceration, moist desquamation, alopecia) and gastrointestinal tract disorders (e.g., vomiting, diarrhea).[23] Information on the long-term effects are lacking, likely owing to overall short survival times.

Doxorubicin may prolong disease-free survival times for cats previously treated with radiation.[31]

Chemotherapy

Indications for chemotherapy include high-grade tumors regardless of surgical margins, detection of metastatic disease, and nonsurgical disease. The benefit of chemotherapy in the microscopic disease setting for FISS is unclear.

Doxorubicin may prolong disease-free survival times for cats previously treated with radiation.[31] Doxorubicin combined with surgery prolonged both the disease-free interval and tumor-free survival time in 21 cats compared with cats undergoing surgery alone; however, the difference was not statistically significant.[32] Administration of 3 doses of epirubicin, followed by surgery and 3 additional doses of epirubicin, resulted in a 14% recurrence rate and 81% cumulative survival beyond 2 years.[32]

Cats with macroscopic tumors that cannot be resected, recur following local treatment, or are otherwise not candidates for surgery, can be treated palliatively with ifosfamide (~3% complete response, 37% partial response), doxorubicin combined with cyclophosphamide (50% partial response), or lomustine (~3% complete response, 21% partial response). Responses to these drugs are brief (median, 2.5 to 4 months), making chemotherapy alone of limited benefit.[33-35] Other drugs, including carboplatin and toceranib phosphate, are ineffective at treating macroscopic tumors.[36,37]

Electrochemotherapy

Electrochemotherapy is the application of short, intense electric pulses to tumor tissue. The pulses transiently permeabilize cell membranes, allowing chemotherapy drugs to have a more potent localized cytotoxic effect. Cats with incompletely excised tumors treated with electrochemotherapy and intravenous bleomycin and intralesional cisplatin had improved tumor-free survival and disease-free interval times compared with a group of historical controls.[38] Electrochemotherapy has limited toxicity and is relatively easy to administer, making it an attractive option for practitioners lacking access to facilities with external beam radiation.

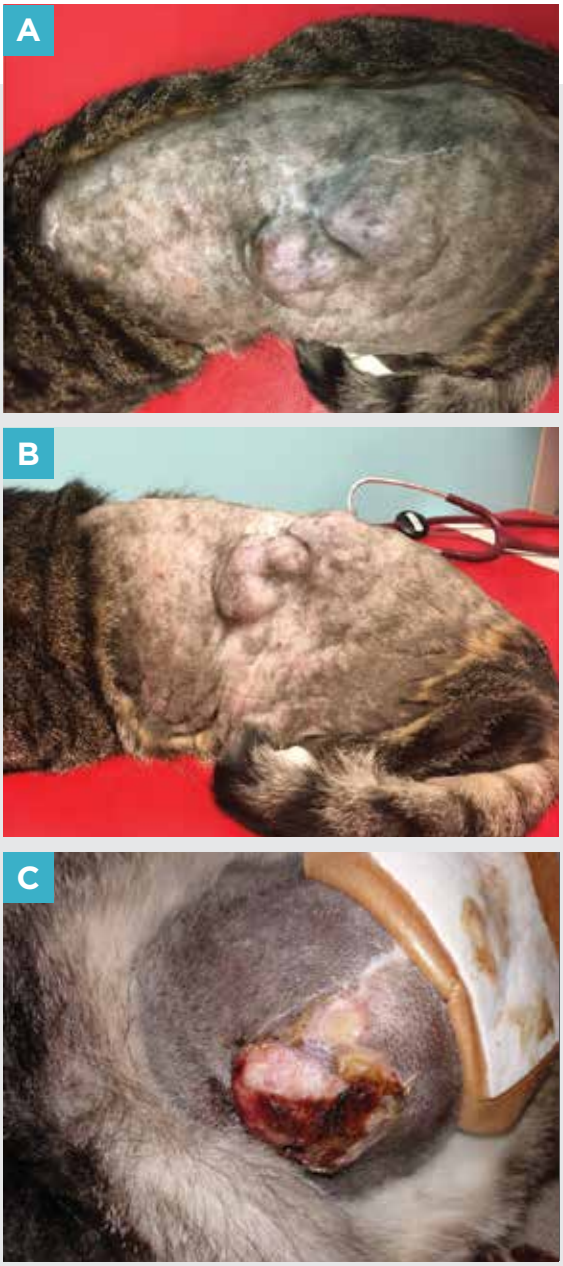

FIGURE 3. (A AND B) Recurrent injection site sarcoma after surgical resection and radiation therapy. In all images, cranial is to the left and caudal is to the right. **(C)** Note extensive ulceration and protrusion of tumor tissue through the skin surface.

CONCLUSION

Perhaps the most intricate aspect of FISS is the knowledge that these tumors can occur secondary to direct measures designed to protect a cat's health. The infectious diseases prevented by vaccinations cause significant morbidity and mortality within the feline population. Rabies is a zoonotic threat to human health. There is no better time than now to acknowledge the benefits vaccines provide. However, the consequences of FISS are frequently devastating, and owners and veterinary professionals struggle with complex emotions surrounding the diagnosis.

FISSs are locally invasive tumors and as such should be treated aggressively. The best outcomes are obtained when an initial radical surgical excision is performed by a surgical specialist. Many cases are optimally treated with multimodal therapy, including surgery, radiation therapy, and chemotherapy. Despite aggressive measures, local treatment failure leading to humane euthanasia within 2 to 3 months of recurrence is the most common cause of death in cats with FISS (**FIGURE 3**). Veterinarians should educate cat owners as to the risk of tumor development.

The authors acknowledge general practitioners may face limitations in referral availability for radical surgery and specialized oncologic care. Owners place constraints as well, sometimes preferring marginal surgeries over more aggressive options. Less radical excisional biopsies ("debulking" surgeries) may be acceptable for owners who will not pursue additional treatment if FISS is confirmed. Clear communication regarding expectations, limitations, and potential negative outcomes is essential in those cases. Cats with suspected FISS should not be monitored—referral to a veterinary oncologist or surgeon is encouraged so owners can be educated as to all options. TVP

Courtesy Tracy Gieger, DVM, DACVIM, DACVR (3)

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CONTINUING EDUCATION

Feline Injection Site Sarcomas: Risk Factors, Diagnosis, Staging, and Treatment Algorithm

TOPIC OVERVIEW

This article presents an overview of injection site sarcomas, including a proposed optimal treatment algorithm that practitioners can follow when managing a patient suspected to have feline injection site sarcoma (FISS). Special focus is given to controversial aspects related to FISS, including risk factors and preventive strategies.

LEARNING OBJECTIVES

After reading this article, practitioners should be able to list risk factors for FISS and describe proposed preventive strategies, develop a diagnostic approach to a cat with suspected FISS, and discuss definitive and palliative therapeutic options along with associated prognoses.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment when approval has been received. To receive credit, take the test for free by visiting **vetfolio.com** and entering the title of the article in the search bar. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **Which of the following risk factors is significantly associated with the development of feline injection site sarcoma (FISS)?**
   a. Needle gauge
   b. Vaccination in the interscapular area
   c. Vaccine temperature
   d. Mixing a combination of vaccines in 1 syringe

2. **Which of the following strategies is recommended by the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF)?**
   a. Administer both rabies and feline leukemia virus (FeLV) vaccines distally on the same limb
   b. Administer rabies vaccines in the distal aspect of the right or left pelvic limb
   c. Administer vaccines subcutaneously in the interscapular region for minimal risk
   d. Administer vaccines as distally as possible on the limb

3. **Which of the following methods is not recommended to diagnose FISS?**
   a. Excisional biopsy
   b. Fine-needle aspiration of the mass
   c. Needle-core biopsy
   d. Wedge biopsy

4. **Which of the following observations should prompt consideration of the "3-2-1" rule in a cat developing a mass in the area of a vaccine?**
   a. The mass persists for 1 month or longer
   b. The mass is or becomes larger than 3 cm
   c. The mass continues to increase in size 2 months following an injection
   d. The mass persists for 3 months or longer

5. **Which of the following is true regarding staging tests for FISS?**
   a. Contrast-enhanced computed tomography (CT) scans estimate tumor volume more accurately than caliper measurements
   b. FeLV/feline immunodeficiency virus (FIV) testing is recommended prior to definitive treatment
   c. Thoracic radiographs are of minimal value because the metastatic rate of FISS is low
   d. Palpation of the tumor on physical examination sufficiently determines tumor size

6. **Which of the following is true regarding surgical excision of FISS?**
   a. FISS is locally invasive and radical surgery is recommended
   b. Marginal surgery in areas not amenable to wide excision is usually curative
   c. Completeness of surgical excision is not prognostically significant
   d. Surgeries performed at referral institutions and nonreferral institutions have similar outcomes

7. **Referral to a specialist is most appropriate when**
   a. Incisional biopsy confirms a diagnosis of FISS
   b. Cytology is suspicious for, but not confirmative of, a diagnosis of FISS
   c. An owner requests an oncologist's opinion
   d. All of the above

8. **Which of the following scenarios outlines the most appropriate use of chemotherapy for treating FISS?**
   a. Completely excised, histologically low-grade FISS and negative staging tests
   b. Metastatic disease detected on presurgical planning CT scan of the lungs and primary tumor site
   c. Owner wishes to treat with toceranib phosphate (Palladia) before considering surgery
   d. FISS recurs 8 months after surgical resection with no staging tests done

9. **Which of the following is accurate regarding prognosis for FISS?**
   a. Prior attempts at tumor excision have not been shown to impact the overall prognosis
   b. Median time to first recurrence is significantly prolonged if surgery is performed by an experienced surgeon at a referral hospital compared with surgery performed at a nonreferral institution
   c. Cats with metastatic disease have similar overall survival times to cats with no evidence of metastatic disease
   d. Histological subtype has no impact on overall survival

10. **How do FISSs differ from non–injection site sarcomas?**
    a. FISSs have a slower growth rate than non–injection site sarcomas
    b. FISSs arise from cutaneous tissues while non–injection site sarcomas arise from subcutaneous tissue
    c. FISSs are extremely locally invasive, much more so than non–injection site sarcomas
    d. FISSs show decreased cellular pleomorphism and mitotic activity on histopathology analysis