HOW TO MANAGE CATS AND DOGS WITH SOFT TISSUE SARCOMAS

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FELINE VACCINE-ASSOCIATED SARCOMAS

Incidence

Vaccine-associated sarcomas (VAS) have been reported to develop at a rate of 0.63 to 3 per 10,000 cats vaccinated annually.[1,2] Evidence points to an increased risk among cats receiving adjuvanted vaccines against rabies and FeLV. There is no association with a specific brand or manufacturer or mixing vaccines in a single syringe, reuse of syringes, needle gauge, temperature of vaccine or massage of the vaccination site.[3] It is appropriate to tell clients there may be a potential risk for their cat developing a VAS but the risk is extremely low. Vaccines afford protection against devastating infectious diseases. In 2007, there were more than 7,000 cases of rabies in the U.S, a 4.6% increase from 2006.; 1 case was a person and 274 cases were cats! Vaccination against rabies must continue. The current AAFP/AFM guidelines for FeLV, however, recommend that FeLV vaccines be only used in those cats at risk of direct exposure to FeLV-infected cats. The prevalence of FeLV is 2.3% and risk factors for infection include outdoor lifestyle, intact males, and a sick health status.[4]

Is Change Good?

Since the implementation of new vaccines and vaccination protocols, there is no data to prove that the incidence of VAS is declining. It is very likely that currently, fewer cats are vaccinated annually for FeLV. There is at least one FeLV vaccine on the market for which the manufacturer reports a 3-year duration of immunity, and there is a licensed needle-less, non-adjuvanted FeLV vaccine. All of this might influence the incidence of FeLV-VAS. Vaccination against rabies has not decreased since sarcomas were first recognized. More likely, the number of cats vaccinated against rabies has increased due to more states requiring it. The non-adjuvanted, canarypox-vectored, recombinant rabies vaccine produces virtually no inflammatory infiltrate at the site of injection[5], however, it must be given annually (as opposed to every 3 years). A needle-less, canarypox-vectored product is now available but it remains to be proven whether these are enough modifications to compensate for the trade-off of a more frequent vaccination.

Table: Adjuvant status of vaccine types available for cats (2008)

Vaccine antigen	Route	Adjuvant status
Panleukopenia (MLV)	SQ, intranasal	Adjuvant-free
Panleukopenia (killed)	SQ	Adjuvanted
Herpesvirus and calici (MLV)	SQ, intranasal	Adjuvant-free
Herpesvirus and calici (killed)	SQ	Adjuvant
FeLV (recombinant)	Transdermal	Adjuvant-free
FIV (killed)	SQ	Adjuvanted
Virulent, systemic feline calici (killed)	SQ	Adjuvanted
FIP (MLV)	Intranasal	Adjuvant-free
Chlamyodphilia felis (avirulent-live)	SQ	Adjuvant-fee
Chlamyodphilia felis (killed)	SQ	Adjuvanted
Bordetella	Intranasal	Adjuvant-free
Giardia (killed)	SQ	Adjuvanted
Rabies (recombinant)	SQ	Adjuvant-free
Rabies (killed; 1-yr)	SQ	Adjuvanted
Rabies (killed; 3-yr)	SQ	Adjuvanted

Evaluation of Cats with Confirmed Sarcomas

Lesions that develop soon after vaccination might be a vaccine reaction as opposed to a tumor. If a sarcoma is confirmed or if the patient's clinical presentation is highly suggestive of a sarcoma, then 3-view thoracic radiographs should be obtained. Metastatic rate for VAS might be as high as 25%. The gross appearance of VAS as determined by physical exam can be misleading. Palpation may suggest the tumor is small and movable. Advanced imaging by use of computed tomography (CT) with IV contrast has dramatically changed how we are able to evaluate tumors prior to surgery. Tumor volume and degree of tissue invasion are usually significantly different from that determined merely by physical exam. It is preferable to offer CT imaging for all patients early in the course of diagnostic work-up. Findings may significantly alter treatment recommendations. CT imaging can be done after a failed attempt at surgical excision. In the post-operative setting, by use of CT we can often identify the extent of the surgical field and use this information to either plan another surgery or radiation therapy. However, this is not ideal.

Surgical Management of Vaccine-Associated Sarcomas

Adequate surgical resection with or without adjuvant external beam irradiation remains the primary treatment for cats with VAS. Initial CT imaging helps to develop a surgical plan. The local invasiveness of most feline sarcomas requires an aggressive surgical approach. Most often, this means excising tumors with 2-5-cm margins; with at least 1 fascial plane below detectable tumor. Incomplete surgical excision may result in a recurrence rate of 30-70%. Recurrence rate might still be as high as 50% even when the histopathology report suggests a complete excision.[6]

Defining the Post-operative Surgical Bed

Many cats are referred to institutions with the ability to combine treatment modalities (i.e. surgery, radiation therapy) prior to the first surgery. This is preferable since it allows a thoughtful, preplanned and coordinated approach to treatment. As previously mentioned, CT imaging prior to surgical intervention is useful to define the surgical plan as well as set-up radiation treatment fields. Placement of metallic markers (i.e. hemoclips, metal sutures, staples) is a relatively inexpensive and easy method to identify the tumor bed during surgical resection. Hemoclips placed at the time of surgery allow radiographic visualization of the full extent of the surgical site. The metallic markers, in conjunction with the surgical scar, would then delineate the surgical volume. Fully understanding the surgical volume aids in planning the radiation target volume if radiation is to be done in the post-operative setting.

Margin Evaluation

Determining margin status is a major prognostic determinant for cats with sarcomas. The entire resected specimen should be submitted for evaluation. Inks and dyes can be used to identify surgical margins and distinguish them from margins created during sample processing. Evaluation of individually marked margins may help planning a second surgical excision or adjuvant radiation therapy.

Surgical Outcome

In one study,[7] 61 cats with VAS were treated by use of marginal (local excision with margins < 3 cm), wide (tumors resected with margins ≥ 3 cm), or radical (limb amputation) excisions, and overall median time to first recurrence was 94 days. Median time to recurrence was significantly longer after radical first excision (325 days) than after marginal or wide first excision (79 days). Overall median survival time for all cats in that study was 576 days.

Radiation Therapy for Vaccine-Associated Sarcomas

Radiation therapy is indicated if CT imaging indicates adequate local control is not possible with only surgery or histologic margins reveal an incomplete resection.

Pre-Operative versus Post-Operative Radiation Therapy

Radiation therapy can be used successfully in both the pre-operative and post-operative settings. The benefits of pre-operative radiation therapy include oxygen enhancement and possibly less patient morbidity. In the presence of oxygen, tumor cells are 2-3 times more sensitive to radiation damage. In general, if radiation is delivered prior to an attempted surgical resection, then the radiation treatment field will be smaller than that of post-operative field. This in turn would lead to irradiation of less normal tissues. Deciding time to initial radiation is best made after discussions with both the oncologic surgeon and radiation oncologist.

Radiation Therapy Outcome

One study[6] of 92 cats treated with radiation therapy before surgery revealed a median time to first event (eg, local regrowth, metastases, or death) of 584 days. Median time to first event was significantly longer when no tumor cells were identified at the margin of the resected specimen (986 days) than when tumor cells were found at the margin of the resected specimen (292 days). Survival as an endpoint was not examined separately in that study[6]; however in another study[8], median survival time for 7 of 25 cats treated by surgery followed by radiotherapy was 842 days.

Chemotherapy for Vaccine-Associated Sarcomas

Chemotherapy might be indicated for non-resectable tumors or when faced with metastatic disease. The clinical benefits of adjuvant chemotherapy in combination with surgery and/or radiation therapy has not been clearly defined.

Cats with Gross Disease

In one study[14], doxorubicin and stealth liposome-encapsulated doxorubicin were evaluated in cats with VAS; response rate was 39% for a median duration of 84 days. Five of 15 cats responded to single-agent doxorubicin and 8 of 18 responded to liposome-encapsulated doxorubicin.[9] The combination of doxorubicin and cyclophosphamide has also been examined in cats with nonresectable VAS; overall response rate was 50% for a median duration of 125 days, but the sample size of 12 cats was small.[10] Carboplatin might prove useful in the treatment of cats with VAS but controlled studies have not been conducted. Ifosfamide chemotherapy is included in the standard treatment of people with sarcomas. We have evaluated ifosfamide in cats with nonresectable, recurrent, or metastatic VAS. In our study, 11 of 27 of cats with VAS had a complete or partial response to ifosfamide. A protocol using saline diuresis and the bladder-protective agent, mesna, must be used when administering ifosfamide.[11] CCNU (lomustine) and imatinib (Gleevec) are other drugs under investigation for treatment of VAS.

Adjuvant Chemotherapy

Cats that ultimately develop metastatic disease have a shortened survival time. In a recent study, the median survival of cats that did not develop metastatic disease was 929 days and that of cats that did develop metastases was 165 days.[12] The benefits of adjuvant chemotherapy, however, have not been clearly defined. In a multicenter study,[9] 75 cats with resected VAS were treated with adjuvant doxorubicin or liposome-encapsulated doxorubicin. When compared with results for a historical population treated by use of surgery alone, cats receiving chemotherapy had a prolonged median disease-free survival time (388 days vs. 93 days). Studies have evaluated use of doxorubicin or carboplatin in addition to surgery/radiation therapy and so far a clear advantage in tumor control has not been found. However, all studies have been underpowered or cats were given chemotherapy after a recurrence of appearance of metastases.[6,8,13]

CANINE SOFT TISSUE SARCOMAS

The clinical presentation of soft tissue sarcomas in dogs is varied and non-specific. Most masses are slow-growing but occasionally a rapid increase in size might occur. The biological behavior is characterized as locally invasive with a metastatic rate that is highly correlated with histological grade (Table).

Table: 75 dogs with soft tissue sarcomas, surgery alone[14]

Mitotic figures (per 10 HPF)	# Cases	% Metastases	Survival (median, days)
< 10	46	13%	1,444
10-19	18	7%	532
> 10	11	41%	236

The gross appearance of sarcomas as determined by palpation alone can be misleading. CT with IV contrast improves tumor evaluation prior to surgery (see cats)

Surgical Management of Sarcomas in Dogs

Initial biopsy and CT imaging helps to develop a surgical plan. Local invasiveness of most sarcomas requires an aggressive surgical approach. Most often, this means excising tumors with 2-5-cm margins; with at least 1 fascial plane below detectable tumor. For some low-grade sarcomas, marginal resection (<1-3 cm margin or not including a fascial plane) might be sufficient, but the consequences of recurrence needs to be thoroughly considered and discussed with each owner of each patient.[15] Refer to sections above regarding *defining the post-operative surgical bed* and *margin evaluation.*

Table: 75 dogs with soft tissue sarcomas, surgery alone[14]

	Extremity		Trunk	
	Complete	Incomplete	Complete	Incomplete
Recurrence	0%	20%	8%	30%

Radiation Therapy for Soft Tissue Sarcomas in Dogs

Radiation therapy is indicated if CT imaging indicates adequate local control is not possible with only surgery or histologic margins reveal an incomplete resection.[16,17] Refer to section above regarding p*re-operative versus post-operative radiation therapy.*

Table: Outcome of dogs with sarcomas treated with radiation therapy.

# Dogs	1-Year Control	2-5 Year Control	Reference
38	73%	68%	Forrest et al. JVIM 14:2000
48	87%	76%	McKnight et al. JVIM 217:2000

Chemotherapy for Canine Sarcomas

Chemotherapy may be indicated for non-resectable tumors or metastatic disease. The clinical benefits of adjuvant chemotherapy in combination with surgery and/or radiation therapy has not been clearly defined but might be appropriate for high-grade tumors. Options include doxorubicin, doxorubicin/cyclophosphamide, ifosfamide, cisplatin or a combination protocol. Metronomic therapy (continuous exposure to low chemotherapeutic dosages) has been shown to inhibit tumor angiogenesis, in one study, low-dose cytoxan and piroxicam delayed tumor re-growth in dogs with incompletely resected soft tissue sarcomas.[18]

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