Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400
VCAwestlaspecialty.com

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH

Lauren Askin, DVM DACVR (Radiation Oncology)
Veterinary Specialist

Etiology/Pathophysiology

Soft tissue sarcomas are a group of tumors that arise from mesenchymal tissues and can originate from visceral and non-visceral sites. Tumors within this group tend to have different morphologic and histologic features, but there biological behavior is similar; therefore they are often treated as one. Several important biologic features have been described that these tumors have in common:

1. Ability to arise from any anatomical site
2. Appear as pseudoencapsulated, but tend to infiltrate through and along fascial planes
3. Metastasize hematogenously in up to 20% cases, but regional lymph node metastasis is unusual
4. Local recurrence after conservative surgery is common
5. Gross tumors generally have a poor response to chemotherapy and radiation therapy

Not all lesions arising from the subcutaneous space are malignant, and many are often benign or inflammatory. Soft tissue sarcomas comprise approximately 15% of all skin and subcutaneous tumors in dogs. Though histologic distinction is not clinically important in the treatment of these tumors, the nomenclature given to soft tissue sarcomas is determined by the connective tissue (muscle, adipose, fascial, fibrous, and neurovascular) from which they arise. Tumors classified as soft tissue sarcomas include fibrosarcoma, peripheral nerve sheath tumor, myxosarcoma, liposarcoma, undifferentiated sarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma. Other tumors also arising from connective tissue such as osteosarcoma, chondrosarcoma, hemangiosarcoma, and synovial cell sarcoma are not classified as soft tissue sarcomas as they have a higher propensity for metastasis.

continued

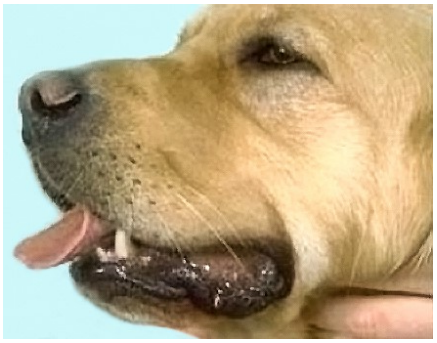
Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

Epidemiology/Signalment

Soft tissue sarcomas tend to occur in middle aged to older dogs with no specific breed or sex predilection; however, medium and large breed dogs do seem to be overrepresented. In dogs, sarcomas have been associated with radiation, trauma, foreign bodies, implants, and the parasite *Spirocerca lupi.*

History and Clinical Signs



Soft tissue sarcomas generally present as firm, fixed, slow growing masses most commonly affecting the trunks, extremities, or oral cavity. Many times they are initially noted when they are small, but go untreated as they are assumed to be benign. The skin overlying these tumors is often moveable and the many times the tumor palpates as an encapsulated mass due to the presence of a psuedocapsule. A pseudocapsule is tissue that has formed from compression of peritumoral connective tissue and may or may not be confluent with tumor cells. When tumors are small, they are non-painful; but as they grow they invade into the deeper tissues which can result in the tumor becoming ulcerated and infected. Clinical signs manifested from the tumor are dependent on the site from where it originates. For example, sarcomas originating in the mouth may cause halitosis, difficulty eating, and salivation; whereas tumors on a limb may result in lameness.

Diagnosis

A fine needle aspirate is always warranted on detection of any new mass or lesion. With soft tissue sarcomas, cytology can be beneficial in helping to rule out cysts or other tumor types (mast cell tumors), but it is always important to keep in mind that cytology is not sufficient for a definitive diagnosis of a soft tissue sarcoma. These tumors do not readily exfoliate and can contain areas of inflammation and necrosis. The presence of inflammatory cells and necrosis in the absence of neoplastic cells on cytology does not rule out a soft tissue sarcoma. A study conducted on FNA's of 40 soft tissue sarcomas reported that only 62.5% of the cases yielded an accurate diagnosis, while 15% of the cases were incorrectly diagnosed.

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

Biopsy and histopathology are needed for definitive diagnosis of a soft tissue sarcoma. There are two approaches to tumor biopsy which include pre-treatment biopsy and post-treatment biopsy. Pretreatment biopsy methods are the preferred methods and include needle core (Tru-cut), wedge or incisional, and punch biopsy. All biopsies performed should be positioned so that the biopsy tract can be included in the curative intent treatment. Post-treatment biopsy refers to an excisional biopsy, where the diagnosis is made after removal of the gross tumor. Many times this method is attractive to clinicians because it allows for treatment and diagnosis in one step; but unfortunately, post-treatment biopsies are rarely curative. Also, the subsequent surgery following an excisional biopsy is many times required to be more aggressive than the surgery required following a pre-treatment biopsy. An excisional biopsy should only be performed when it is possible to take a 2-3 cm margin around the tumor.

Once a diagnosis of soft tissue sarcoma has been made, it is important to determine the clinical stage or extent of disease. Knowledge of the clinical stage of the tumor will help determine the appropriate treatment. Diagnostic tests that should be performed prior to beginning definitive treatment include 3-view thoracic radiographs, as the lungs are the most common site of metastasis for soft tissue sarcomas. Also, careful palpation of the regional lymph nodes is important. If the draining lymph node palpates enlarged, a fine needle aspirate or biopsy of the lymph node should be performed. Careful palpation of the mass is necessary to determine the tumor size and fixation to surrounding tissues. Advanced imaging with the use of computed tomography or magnetic resonance imaging can be helpful to evaluate the extent and invasiveness of larger tumors, tumors in the head or neck, or tumors within a body cavity.

Therapy

Surgery

Local tumor control accomplished with wide, surgical excision is considered the treatment of choice for soft tissue sarcomas, and advances in reconstructive techniques have significantly expanded surgical options for aggressive resection with good functional and cosmetic outcomes The surgical approach for soft tissue sarcomas has been classified according to the extent of the wound margins as intracapsular (when the tumor is surgically penetrated); marginal (when the tumor is excised just outside, or at, the pseudocapsule); wide (when a

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

portion of normal tissue is left around the tumor); and radical (when an entire anatomic segment is removed, for example, amputation). The minimum recommended margins for surgical resection are 3 cm lateral to the tumor and one fascial plane or 3 cm deep to the tumor. However, if the tumor has attached to the muscle layer or fascial layer, the entire layer may be compromised and should not be considered a clean margin. Also, fat and connective tissue do not serve as good tumor barriers, so if the tumor overlies these structures, the 3 cm rule for margins should be utilized. Biopsy tracts and any areas of fixation to surround tissue should also be resected *en bloc* with the tumor, as these areas are considered to be contaminated.

Soft tissue sarcomas are typically surrounded by a pseudocapsule, which creates an easy plane of cleavage between the tumor and surrounding tissues allowing the tumor to be "shelled out" and submitted for histologic evaluation. Unfortunately, this type of marginal excision commonly results in tumor cells extending to the edges of the resected tissue. Any surgical procedure involving margins <2 to 3 cm in all directions must be considered an incomplete excision even if no macroscopic tumor is evident after removal.

Histopathology of the tumor and surrounding tissue following surgery is important as it provides surgical margins and tumor grade; and both are necessary in determining whether further treatment including surgery or radiation therapy is necessary. Following removal of the tumor, surgical margins should be clearly marked on the specimen and completeness of excision should be evaluated. The resected tumor should be pinned out to the original dimensions to prevent shrinkage during formalin fixation. It has been recommended that the following terminology be used for margin evaluation:

1. Incomplete margins: Neoplastic cells are continuous with at least one surgical margin in any plane.
2. Close margins: Distance between surgically created tissue edge and neoplastic cells is less than 3 mm thickness, or surgical margins do not contain normal tissue outside the pseudocapsule.
3. Complete margins: Distance between surgically created tissue edge and neoplastic cells is at least 3 to 5 mm.

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH

continued

Marginal and incomplete surgeries are usually associated with a higher risk of local recurrence (26-60%) and dogs with incomplete margins are 10.5 times more likely to develop local recurrence than dogs with complete margins. Studies have also shown that the first surgery provides the best opportunity for local tumor control, as subsequent surgeries increase morbidity, treatment costs, and the risk of further local tumor recurrences, while decreasing survival time. If a second surgery is performed following inadequate resection, a margin of healthy tissue of 3 cm in all directions is recommended, including removal of normal appearing subcutaneous fat and underlying fascia. The entire surgical wound is contaminated and should be considered neoplastic. In a study evaluating scar re-excisions, local recurrence was reported in 15% of dogs and residual tumor was identified in 22% of the resected scars.

Surgery and Radiation Therapy

Prior to the routine availability of radiation treatment, radical and often disfiguring surgery was the mainstay treatment for soft tissue sarcomas which resulted in 1-year control rates of 70-80%. Although soft tissue sarcomas have historically been considered radiation resistant when compared to other tumor types, a multimodality approach of surgery and radiation therapy has proven to help prevent local recurrence.

Varian 2100 EX Linear Accelerator (LINAC)

The sequencing of radiation and surgery is based on multiple factors and should be determined on an individual basis. There are several advantages and disadvantages to both preoperative and postoperative radiation therapy. The rationale for administering postoperative radiation therapy is that the radiation kills or prevents the multiplication of any microscopic tumor cells left behind. Some advantages of postoperative radiation include 1) wound complications are rare in tissues that are irradiated after the first inflammatory phase of wound healing; 2) removal of a larger tumor with necrotic regions or infections may make the patient and patient's family more comfortable; and 3) postoperative treatment planning may be simpler than preoperative planning in patients in which the size or shape of a tumor creates

continued

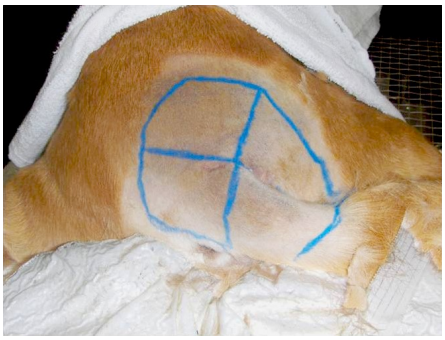
Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

difficulty in achieving a uniform dose distribution. Disadvantages of post operative radiation include 1) increased radiation field sizes; 2) damage to vasculature, which may lead to hypoxia decreasing the effectiveness of radiation; and 3) potential delays in the start of radiation therapy if post-surgical wound complications occur. Post-operative radiation is generally started within 7-14 days after surgery.

The rationale behind preoperative radiation therapy is to inactivate the large number of peripheral tumor cells reducing the contamination of the surgical site. Advantages to preoperative radiation include 1) a smaller radiation field; 2) possible shrinkage of the tumor making surgical excision with wide margins less difficult; and 3) undisturbed tumor bed and blood supply increasing effectiveness of radiation. While disadvantages to preoperative radiation include the possibility of poor or delayed wound healing in the irradiated field. Generally, preoperative radiation is reserved for tumors that are initially determined to be inoperable.

Radiation therapy is commonly is used as an adjunct to surgery. Radiation seems to have the greatest efficacy when it is used to treat remaining microscopic disease following surgical cytoreduction of a soft tissue sarcoma; and it is less effective when used to treat bulky, gross disease. Marginal surgical resection combined radiation therapy is an attractive alternative to limb amputation for a soft tissue sarcoma on an extremity. It also can be used following a planned marginal resection when wide surgical resection is not possible such as with tumors of the head or neck. In these cases, removal of all grossly visible tumor is completed. Radiopaque clips are often placed during surgery marking the lateral, proximal, and distal extent of the tumor to aid in radiation planning.



Basic set up for an incompletely excised STS treated with electrons.

Several studies have been done evaluating radiation therapy for incompletely excised soft tissue sarcomas in dogs. Studies have shown that similar local control and survival rates are attained with a better functional and cosmetic outcome by performing marginal surgical excisions plus adjuvant radiotherapy compared to radical surgery alone. A prospective study was performed which evaluated 48 dogs with soft tissue sarcomas treated with surgery to decrease disease to <3 cm followed by full course radiation therapy to a total dose of 63 Gy. This study

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

reported a 5 year survival rate at 76% and a recurrence rate of 16%. The median time to recurrence was 23.3 months. Another study evaluating 35 dogs with soft tissue sarcomas that were excised to microscopic disease followed by daily radiation to a total dose of 42-57 Gy reported an overall median survival of 61.7 months.

A recent study completed in 2012 evaluated intentional marginal excision of canine soft tissue sarcomas of the limb followed by a coarsely fractionated radiation protocol consisting of four 8 to 9 Gy fractions at 7- day intervals. Fifty-six dogs were included in the study. The results of this study compared favorably to studies using more fractionated “definitive” protocols, as the 1-, 2-, and 3- year disease-free intervals were 82, 74, 70%, respectively, and a local recurrence rate of 18%. The main disadvantages of using coarsely fractionated protocols are reduced efficacy and the increased risk of late radiation toxicity, which may be significant and include bone necrosis and radiation induced tumors at the site. This study supports, however, that in the postoperative setting coarsely fractionated radiation protocols can give good control and that the risk of late radiation side effects is low when the fraction size does not exceed 8 Gy.

Radiation Therapy

If surgical excision of a soft tissue sarcoma is impossible because of tumor location or size of the tumor, primary radiation therapy can be applied; however, measureable and bulky tumors tend to have a poor long term response to primary radiotherapy. Long term control of soft tissue sarcomas with conventional doses of radiation alone (40-48 Gy) are difficult to obtain because of their low growth fraction, relatively long doubling time, and tendency to develop hypoxic regions within the tumor parenchyma. Reported 1-year control rates are 30% at 35 Gy (10 x 3.5 Gy), 35% at 40 Gy (10 x 4 Gy), 48% at 45 Gy (10 x 4.5 Gy) and 67% at 50 Gy (10 x 5 Gy). At 2 years, control rates vary from 12% at 40 Gy and 33% at 50 Gy.

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

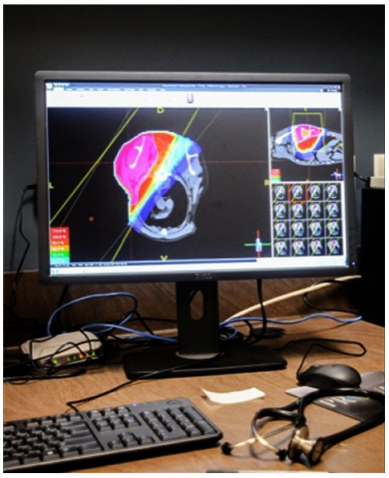
As a single modality, radiation is generally considered palliative for soft tissue sarcomas with control defined as a slowly regressing or stable-in-size tumor mass. The goal of palliative or coarsely fractionated radiation therapy is alleviate pain, swelling, and inflammation associated with the tumor, in hopes to improve quality of life. Typical palliative protocols involve large radiation doses (5-10 Gy) delivered as a few fractions once or twice weekly. The delivery of a small fraction size once per week is unlikely to lead to a durable response because tumor cells have a significant amount to time to repair damage and proliferate between treatments. Therefore, larger doses of radiation are often delivered to optimize killing of tumor cells, with the increased risk of late radiation toxicity accepted as part of the treatment. Since palliative radiation therapy is administered to improve quality of life, not prolong life, patients will likely live long enough to experience permanent late effects. Control rates for soft tissue sarcomas treated with palliative protocols have been reported to be greater than 87% with time to progression ranging from 5.2 months to 8.8 months.

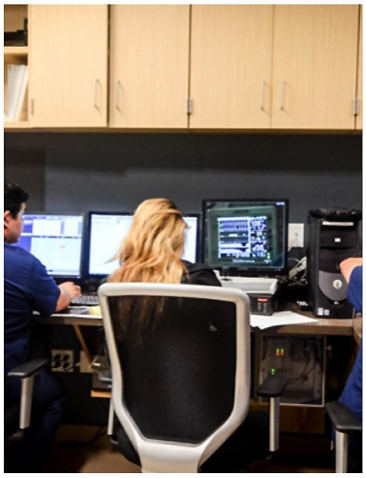
A retrospective study completed in 2012 evaluated a palliative radiation protocol consisting of 4 Gy fractions given over 5 consecutive days, as the concern for clinically significant late effects of palliative radiation protocols can be addressed by delivering lower doses of radiation. In this study, 10 soft tissue sarcomas were treated. A measurable overall response rate of 80% was reported with tumor control achieved in 100% of patients, and a median progression free survival of 5.7 months. With this protocol, the risk for late side effects is about half that of the traditional 8 Gy x 4 fraction protocol; therefore, retreatment with the 4 Gy x 5 fraction protocol may be considered without more concern for toxicity than a single traditional 8 Gy x 4 fraction protocol.

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*





Dr. Lauren Askin with her patient, Shaka, who is undergoing radiation therapy for his soft tissue sarcoma (STS).

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

Chemotherapy

Adjuvant chemotherapy at times is useful in the treatment of soft tissue sarcomas. Chemotherapy is best used when combined with radiation therapy and/or surgery. Chemotherapy alone does not seem to be effective for measurable soft tissue sarcomas, with the exception of providing palliation in some cases. Doxorubicin-based protocols, either alone or in combination with cyclosphasmide have shown the most promise with an overall response rate of 23%.

Despite the fact, that generally soft tissue sarcomas are slow to metastasize, the metastatic rate for cutaneous soft tissue sarcoma is grade dependent and varies from less than 15% for grade I and II soft tissue sarcomas to 41% for grade III soft tissue sarcomas. Due to the higher metastatic rate of grade III soft tissue sarcomas, post-operative chemotherapy should be considered as it may prevent or delay metastasis. Single-agent doxorubicin, mitoxantrone, or combination protocols are most commonly used.

Metronomic chemotherapy, continuous administration of chemotherapy drugs at doses that are significantly lower than conventional maximally tolerated dose therapy, has also been evaluated in canine soft tissue sarcomas. A retrospective study was done in 2008 which evaluated 85 dogs with incompletely resected soft tissue sarcomas. Thirty of the these dogs received continuous Cyclophosphamide (10mg/m2) and standard dose piroxicam therapy (0.3 mg/kg) and 55 control dogs did not receive additional therapy. When comparing these two groups, treated dogs had a disease free interval of 13.7 months which was significantly longer when compared to 7.0 months for untreated dogs. Another study completed in 2011 evaluated low-dose cyclophosphamide and its effects on T regulatory cells and tumor angiogenesis in dogs with soft tissue sarcomas. This study found that those dogs receiving 15 mg/m2/d of cyclophosphamide had significant decreases in the number and percent of T regulatory cells as well as the microvessel density, further supporting that metronomic therapy may provide antitumor effects.

continued

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

CANINE SOFT TISSUE SARCOMAS: BRIEF OVERVIEW AND RECOMMENDED THERAPEUTIC APPROACH *continued*

Prognosis for Dogs

The overall prognosis for dogs with soft tissue sarcomas is good, but the range of biological behavior for these tumors can be broad. The median survival time for dogs with soft tissue sarcoma ranges from 3.9 years following surgery alone to 6.2 years with surgery and adjunctive radiation. Overall, up to 33% of dogs eventually die of tumor-related causes.

Research has identified valuable prognostic information from histologic grade, mitotic index, and completeness of surgical margins. Complete margins predict non-recurrence; and recurrence appears to increase with grade. The metastatic rate for dogs with grade I or grade II soft tissue sarcomas is less than 15% compared to 41% for grade III soft tissue sarcomas. High mitotic index (> 9 mitotic figures per 10 high power fields) is prognostic for reduced survival. Other factors, including markers of cellular proliferation, tumor dimension, tumor location, histologic type, invasiveness, and cytogenetic profiles may be useful indicators of prognosis, but presently require further investigation.■

Radiation Oncology
VCA West Los Angeles Animal Hospital
1900 S. Sepulveda Boulevard
Los Angeles, CA 90025
P 310-473-2951 | F 310-979-5400

Lauren Askin, DVM, DACVR (RO)

Veterinary Specialist
VCA West Los Angeles
Animal Hospital

Dr. Lauren Askin was born and raised in West Virginia. She attended the University of Delaware where she received her Bachelor's degree in Animal Science in May 2005. She earned her DVM at the University of Georgia in 2009. Following completion of Veterinary School, she completed a one-year small animal medical and surgical internship at VCA West Los Angeles. Dr. Askin completed a 2-year residency in Radiation Oncology at North Carolina State University and is board certified in veterinary radiation oncology. Dr. Askin's interests include advanced radiation therapy techniques to improve local tumor control and reduce treatment related side effects.