

O - Oncology

SARCOMAS OF SOFT TISSUES

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INTRODUCTION

Sarcomas of soft tissues (STS) are common in companion animals and pose a therapeutic and diagnostic challenge for the practising veterinarian. STS is defined as a malignant tumour of the extraskeletal connective tissues. These tissues, all of mesoderm origin, surround, support or connect other anatomic structures and are present in any part of the body. Because soft tissues are estimated at 40% proportional body weight, it is not surprising that numerous soft tissue tumours arise with regularity. STS form an assembly of tumours of different histogenetic origin, with ubiquitous localisation possibilities, and variation in biological behaviour. Still, STS are often grouped together because of their shared mesodermal origin, similarities in clinical presentation, and communality in diagnostic and therapeutic approach.

In general, STS are fleshy (the Greek word 'Σάρκωμα' or 'sarkoma' is often translated as flesh-like mass), infiltrative and locally aggressive tumours that have a variable metastatic potential. This chapter will describe the common STS in dogs and cats. Visceral and other organ-specific STS (e.g., splenic hemangiosarcoma) will be discussed in the representative chapters.

INCIDENCE

STS are common tumours and comprise from 15% (skin and subcutaneous tissues) to 35% (spleen) of all canine tumours, dependent on original tumour location. Cats are afflicted less frequently (7% reported for skin and subcutaneous tissues). The annual incidence of STS in the United States is estimated to be 35/100.000 for dogs and 17/10000 for cats at risk. These data are not available for the European countries.

EPIDEMIOLOGY

Little is known about the pathogenetic cause of STS in dogs and cats. Changes in genetic make-up, chronic trauma, foreign bodies, vaccinations, parasites and radiation have been associated with STS in both species. P53 mutations and MDM2 gene amplification were observed in a subgroup of canine soft tissue sarcoma; however, familial predispositions have not been reported. No sex or breed predilections have been found, although certain breeds seem to be afflicted with tumours more commonly than others. For example, retrievers seem predisposed to development of soft tissue sarcomas of the head (oral cavity/mandibular/maxillary region) with often a low grade histologic appearance but high aggressiveness. Whether STS predisposition is caused by a breed-specific genetic abnormality or by a high inbreeding coefficient due to the popularity of the breeds, is at present unknown. In general, most studies report medium to large breeds to be affected more commonly, with a overrepresentation of the older animal. Trauma was associated with the incidence of STS. It is unclear if trauma causes an owner to be more aware of problems in that area or if trauma is an initiating cause in STS. The presence of foreign bodies or material (such as vaccinations) may induce chronic stimulation of the tissues and promote neoplastic transformation. An example of this is the parasitic infestation of *Spirocerca Lupi* and the incidence of oesophageal cancer. Radiation has also been associated with sarcoma formation, although sarcoma formation after extracorporeal therapeutic radiation seems to be rare.

CLASSIFICATION

All soft tissues are exposed to the risk of benign or malignant tumour formation. Extensive

classification schedules are available from human literature and are simplified to fit into the companion animal situation (Table 1). Any classification schedule, however, is complicated by overlapping patterns of dedifferentiation or by the inability to recognize the appearance of the cell of origin. A classification by localisation, grade and tumour stage seems more logical and may prove more useful at present. Advances in histochemical, electron microscopic and biogenetic markers will improve the ease of classification in the future. Muscle actin, desmin, vimentin, factor VIII antigen and lysozyme are suggested to be useful for the differential diagnoses of STS, and cytokeratins for synovial cell sarcomas specifically.

DIAGNOSIS

The diagnostic plan for STS is not essentially different from any other tumour type. The physical appearance is noticed depending on the location of the tumour and, in general, peripherally-located tumours are more easily detected and often smaller than more centrally-located STS. Clinically, STS often are solid masses that seem well-circumscribed and encapsulated. However, this is based upon the presence of a pseudocapsule of atrophic remains of surrounding tissue and wedged tumour cells, while infiltration through this pseudocapsule and through fascia leads to attachment to deeper structures.

Pain is associated with location, pressure of the tumour or tumour invasion. Some peripheral nerve sheath tumours have been reported to be sensitive to the touch. A clinical differentiation between benign and malignant is not possible, so additional diagnostics are necessary. Moreover, rate of growth of the tumour often does not predict the biologic behaviour correctly. Additional biopsy specimens should be obtained in all cases. The easiest method of biopsy is fine needle aspiration (FNAB), and this method should be used as the first step in the diagnosis. Although many STS are not well-diagnosed by FNAB because of their limited exfoliative character, many other tumour types can be excluded as well as some inflammatory processes; in particular if infection can be demonstrated while overlying skin is intact. Chronic traumatic inflammation as cytologic diagnosis of FNAB should fit with history and site. In case of any doubt, and in particular also if cytology indicates mesenchymal proliferation in absence of an inflammatory response, this provides a solid indication for further diagnostic work-up. Incisional, excisional or thick needle core biopsy (TNCB) specimens should be obtained. TNCB is the easiest and fastest method and requires minimal sedation.

Multiple core biopsies should be performed and submitted to the pathologist. Sufficient tissue, however, is often better acquired by incisional or excisional biopsies. Excisional biopsies are only advantageous when adequate margins can be obtained. In all other cases an incisional biopsy is preferred. Normal tissue should be incorporated in the biopsy specimen to evaluate peripheral infiltration of the tumour. Incisional biopsies should always be performed in such a manner that removal of the scar is possible in future radical excisions or adjunctive radiation therapy protocols. Adjunctive diagnostic evaluations should include routine blood work, radiographs of the local tumour site for possible underlying bone infiltration, ultrasound of the tumour, radiographs of the chest for possible metastatic spread, FNAB of the regional lymph node and CT or MRI imaging techniques.

In evaluating soft tissues, MRI has many advantages over CT imaging, however, is often not available or cost-effective. A pulmonary CT scan is preferred above plain radiographs. Although haematogenous spread of STS is more common, undifferentiated STS may spread to regional lymph nodes, warranting evaluation of these lymph nodes. For example, synovial cell sarcomas are often reported to spread through the lymphatics. Proper imaging should be performed of more centrally-located lymph nodes along the lymphatic tract, in cases of suspected or proven metastasis to the regional lymph node. For example, metastasis to regional lymph nodes in the limb or inguinal area, should be followed by ultrasound examination of the internal iliac area. In addition, there are indications that splenic metastases are not uncommon in cases with synovial cell sarcomas.

The most important factors in STS evaluation are the determination of tumour grade and tumour stage. Tumour grade is determined through histological evaluation and varies among grade I (low grade or well differentiated) to grade III (high grade or poorly differentiated). Tumour grade is determined by degree of differentiation, cellular pleiomorphism, cellularity and matrix formation, as well as mitotic index and amount of tumour necrosis. Experienced pathologists may apply a different weight to the respective factors in different types of STS to assess tumour grade. In human sarcomas, the tumour grade has a major impact on tumour staging. Tumour staging is based on four parameters: histological grade (G), tumour size (T), regional lymph nodes (N), and distant metastasis (M) (Table 2). Factors reported to be of prognostic importance in canine STS are size, site, grade and presence of local or distant metastases. The prognostic effect of localisation

of the tumour is most likely dependent on the difficulty of complete excision. The higher the stage of the disease, the poorer the prognosis

GENERAL CONSIDERATIONS

STS pose a problem to the veterinarian mainly because they tend to be locally aggressive. Complete surgical excision is often impossible because of localisation or size of the tumour. Recurrence is common after incomplete resection and is the primary reason to refer STS to the Utrecht University Surgical Oncology Service. Most recurrences will occur within 2 years after primary tumour removal. Recurrence is caused because STS tend to spread into deeper or surrounding tissues by invasion or extension next to natural anatomic structures. These finger-like outgrowths of the tumour are often compared to the tentacles of an octopus. Cutting of the tumour mass (cf. body of the octopus) leaves these tumour extensions (cf. tentacles) in the patient. Through this, the tumour homeostasis is disrupted and fast growing tumour cells thrive causing fast tumour regrowth. Early detection and diagnosis of the original STS will facilitate complete removal and prevent recurrence. Shelling out STS is the most common cause for recurrence. Education and communication should be directed in the future to achieve these goals of early detection and complete removal.

Overall metastatic rate is estimated to be 20%. Among STS subtypes there exists considerable variation. In part, this appears based on a link between subtype and frequency distribution of histologic grade. Low to moderate rate of metastasis is seen in (mostly low grade) hemangiopericytoma and the closely related malignant peripheral nerve sheath tumour. Similarly, a low to moderate rate of metastasis is seen in most fibrosarcomas (the subgroup of oral cavity/mandibular/maxillary fibrosarcomas is the exception to the rule). Synovial cell sarcoma and undifferentiated sarcomas are more frequently of high grade and have a relatively high rate of metastasis, i.e., 40-60%. Rhabdo or leiomyosarcomas are relatively less common, and liposarcomas are rare; these last subtypes have a moderate rate of metastasis, except for embryonal rhabdomyosarcoma (high rate).

Metastases spread by haematogenous routes and lymph node involvement is reported to be rare. High grade tumours, such as synovial cell sarcoma and rhabdomyosarcoma have an higher incidence of lymphatic spread especially in late stages of the disease.

HISTOLOGICAL SUBTYPES

Fibrosarcoma

Fibrosarcoma (FSA) was the most commonly diagnosed STS. The recent more complete pathological differentiation in subtypes, however, will decrease the total number of 'pure' FSA in dogs and cats. For instance, neuroFSA, a diverse group of tumour types derived from fibroblast associated with nerves, are currently grouped under the nomenclature malignant peripheral nerve sheath tumours (PNST) instead of under FSA. Per definition, FSA are tumours derived from the fibrocytes. FSA are relatively more common in the cat than in the dog and have a locally-aggressive behaviour. They can occur anywhere in the body, but are most commonly seen in the skin and subcutaneous tissues and the oral cavity. The canine, histologically-low-grade-and-biologically-high-grade, FSA, located in the oral cavity, and mandibular and maxillary region, is a tumour that should be mentioned specifically. This tumour, most commonly associated with young dogs, has an aggressive biological behaviour, whilst diagnostic surgical biopsies depict a low histological grade. Feline FSA occur often on the limbs in older animals without a sex or breed predilection.

Malignant peripheral nerve sheath tumours (PNST)

Malignant PNST contain a group of tumours with varying nomenclature. Included in this group are neurofibrosarcoma and malignant schwannoma. PNST are locally aggressive and metastasise rarely (in less than 20% of the dogs). Metastasis rate is dependent on tumour grade, however. It is unclear at this moment what the cell of origin is in these tumours (i.e., fibrocytes or Schwann cells). PNST can occur anywhere in the peripheral nerve system. The most common location is the subcutaneous tissues of the distal extremities in the dog. PNST located in the closer proximity to the vertebrae (including those in the region of the *plexus brachialis*) often will cause nerve compression and signs of pain and neurological deficit. Invasion of these tumours into the spinal cord is not uncommon and may be seen in over half of cases of high histological grade. Before surgery, a CT-scan (or MRI) of the region is advised.

Haemangiopericytoma (HPC)

Haemangiopericytomas (HPC) were believed for long to stem from pericytes (cells with contractile properties surrounding small blood vessels), though proof is lacking for this histogenetic origin. HPCs form a whorl-like growth pattern

at histological examination without visible connection with nerves. Biological behaviour of HPCs is similar to that of PNST, and many will stain positive for the immunohistochemical marker S100, indicating peripheral nerve origin. Therefore, some authors group HPC under PNST. HPC often have a slow rate of growth, yet are locally aggressive (infiltrative), but have a low (<15%) rate of metastasis. Older dogs (with boxers predisposed) are affected, and HPC consists of 5% of all skin and subcutaneous tumours. Most HPC's are located on the extremities.

Myxosarcoma

Myxosarcoma are FSA containing connective tissue cells that produce intracellular mucin. These tumours are often soft to the touch, but behave similarly to other FSA, in which tumour grade is the most important predictor of behaviour.

Haemangiosarcoma (HAS)

HSA are common tumours that arise from endothelial cells of blood vessels. HSA commonly are located in body cavities and are of extreme aggressiveness (see related chapter). Somewhat less common, they originate of capillaries in dermis, subcutis or deep-seated tissues, including muscle or even bone.

Dermal/subcutaneous HSA have been reported in certain breeds (Whippet, Saluki, Blood Hound, pointers) and may be associated with exposure to ultraviolet light. Predilection sites include abdomen, prepuce and hind legs. Rupture of bad-quality, tumorous blood vessels is not rare, and may lead animals to be presented with haematoma, with or without knowledge by the owner of a pre-existing lump in the same area. Behaviour of extracavitary HSA depends on location and size. Strictly dermal HSA without invasion have a fair prognosis, with assessments of less than a 25% rate of metastasis. High rates of metastasis are seen with invasive lesions and with those of deeper anatomical location. Multifocal manifestation of HSA is not only seen with visceral forms, but also sometimes at dermal/subcutaneous sites, posing a major problem in the therapy. Dermal (stage I) HSA are small tumours, often located in the ventral-abdominal or preputial region, and associated with longer survival times (median survival 780 days) than the hypodermal (stage II) and deep muscular (stage III) located tumours. The deep muscular HSA have a larger size, do not have an anatomical predilection, and generally have a shorter survival (median survival 172 and 307 days, respectively). The majority of the cutaneous HSA, however, are superficial tumours. There appears to be some influence of hair length and skin colour. Dogs with short hair coats and

lightly pigmented skin have more dermal type of HSA, less subcutaneous types, and more HSA of ventral smooth and hairless skin.

Liposarcoma

Liposarcomas are rare, malignant tumours derived from fat cells. Liposarcomas are observed in older animals and may be associated with foreign bodies or obesity. Liposarcomas are often firmer than 'normal' lipomas, are poorly defined and often occur in the ventral region of the body. Biological behaviour is characterised by local infiltration and early metastasis. Infiltrative lipoma is a form that is described in the dog and is comparable with the human well-differentiated liposarcoma. They have an infiltrative behaviour and are difficult to remove locally because of their infiltrative nature. Infiltrative lipomas are often observed in the muscles of the front and hind legs. Infiltrative lipomas can only be distinguished from benign lipomas if muscle invasion is present histologically. Clinically, they appear more attached to the deeper structures and less encapsulated.

Lymphangiosarcoma

Lymphangiosarcoma are rare tumours of the lymph vessels. Although often described in young animals, they can affect dogs and cats of all ages. The ventral thorax and abdomen is a predilection site of the cat. The tumours have a soft and cystic like appearance and may coincide with peripheral oedema. Lymph fluid may 'sweat' through the skin of affected sites. Lymphangiosarcomas are invasive and have a high metastatic potential

Leiomyosarcoma

Malignant transformation of smooth muscle cells are the origin of leiomyosarcoma. They can occur in any part of the body, but are described as firm, lobulated masses most commonly associated with the digestive tract from oesophagus to rectum or the urogenital tract. Clinical signs may relate to obstruction or bleeding due to ulceration. Transformation of benign leiomyomas to leiomyosarcomas has been suggested but not scientifically proven. Leiomyosarcomas are infiltrative tumours that metastasise late in the disease process. Multiple leiomyosarcomas are possible and warrant thorough examination of the abdomen before or during the surgery. Paraneoplastic hypoglycaemia has been associated with leiomyosarcoma.

Rhabdomyosarcoma

Rhabdomyosarcoma, a tumour from the striated muscle cells, is relatively rare in the dog. Two forms have been described: the first occurring in

the urogenital tract of young dogs (mainly bladder) and is referred to as juvenile-type or botryoid rhabdomyosarcoma. The second form occurs in the older animal and is described affecting the tongue, pharynx, myocard and rarely other skeletal muscle locations. Rhabdomyosarcomas are locally aggressive and metastasise early.

Synovial cell sarcoma

Synovial cell sarcoma (SCS) are tumours that arise from tenosynovial tissue and are often associated with lameness. Predilection sites are the stifle and elbow joint but other locations near joints, tendons or bursae have been described. Also, in this tumour type, the origin of the tumour cell is not clear (synovial cell versus periarticular connective tissue cell). Histologic typing may divide those with one-cell population (monophasic) from those with two-cell populations (biphasic), with either one being epithelial-like, the other mesenchymal. Immunohistochemistry often demonstrates a positive signal for both cytokeratins as well as for desmin, reflecting the mixed differentiation. Local invasion of underlying bone is common in later stages of the disease and is easily recognisable on routine radiographs by punched-out bone lesions. The tumour invades the bone at the attachment of the joint capsule or tendons to the bone. SCS are locally aggressive and metastasise late in the disease process. Metastasis rates of up to 50% have been reported, again depending on tumour grade. SCS metastasise to lymph nodes, lungs, spleen and liver.

TREATMENT

Surgery is the primary therapy of STS, with or without adjunctive therapy. The surgical goal is to completely remove the STS and, as a result, a large margin of normal tissue is sacrificed. An example of this type of surgery is the amputation of a limb. Limb-sparing surgeries are an alternative, but can only be performed in combination with adjunctive therapy modalities such as radiotherapy, chemotherapy and immunotherapy.

Surgery

Surgery is only successful if large margins of normal tissue are obtained, with margins of 2-3 cm normal tissue advocated. The objective local failure rate for marginal excisions (peel-out or shelling-out STS) in humans is 86%; however, these rates, based on large numbers, are unknown in dogs and cats. Failure rates after wide local excisions and more radical excisions (such as amputations) were 49% and 14% in humans, respectively. Extrapolation from human data is tempting, but should be interpreted with caution. Recurrence rates of 60-

70% are reported in marginally-excised, canine haemangiopericytomas and STS. Although most STS tend to recur within a year after surgery, adequate follow-up of 2 to 3 years is necessary. Wide surgical excision is often complicated by the anatomic localisation of the tumour to important structures. In these cases a more conservative surgery is planned (eg. limb spare). The owner should be made aware of the increased chance of recurrence compared to radical excision. In general, a repeat surgery is more complicated if the STS has recurred and failure is more likely. The first surgery has the largest chance for complete removal. Recurrence, as of yet, is not associated with an increased risk of metastases, however. It is the authors' opinion that the incidence of metastases depend more on tumour grade than on the type of surgery performed. The recurrence rate decreases when the surgery is performed by more experienced oncologic surgeon. Experience often correlates to a more radical surgery, knowledge of innovative reconstruction techniques and better understanding of the pathophysiological properties of the tumour.

Radiation therapy

Conventional techniques of radiation are rarely successful, while fractionated radiotherapy as a sole therapy using megavoltage irradiation yields a one-year control of about 50-60%. Radiation therapy is associated with acute-onset and with chronic side effects. Radiation is more effective with minimal (microscopic) disease than with more bulky disease. Radiation in combination with surgery results in increased disease free intervals. The radiation therapy is used to treat the microscopic disease left behind after marginal excision of the tumour bulk, achieving identical results compared to radical excision (80-90% at 2 years). Forrest, et al. (J Vet Med Intern 2000) showed a median time to recurrence after incomplete excision of STS and radiotherapy of 798 days. Of STS-subtypes, HPC seems relatively sensitive. Surgical excision and radiotherapy did not increase median tumour-free and survival times compared to complete excisions in feline FSA. Most cats of the first group had incomplete (dirty) surgical excisions, however. Radiation has also been used in combination with local or whole-body hyperthermia. The addition of whole body hyperthermia was not associated with a better local tumour control, and most dogs experienced local failure or metastatic disease. Two-year recurrence free rates of approximately 30% were described.

Intraoperative radiotherapy has been described to cause STS formation in approximately 20% of dogs treated.

Chemotherapy

Chemotherapy can be used to treat local and systemic disease. Chemotherapy is used for palliation in macroscopic and may be of limited benefit in eliminating microscopic local or metastatic disease in STS. Multidrug chemotherapy protocols, including anthracyclines (doxorubicin, mitoxantrone), have been advocated as the most successful. Combination therapy of an anthracycline with vincristine and cyclophosphamide appear more effective in a limited series of STS. The scientific data supporting the efficacy of these protocols in dogs and cats are currently missing, however. More randomised studies using large populations evaluating the effect of chemotherapy are necessary.

Immunotherapy

The treatment of STS with immunotherapy is under review at Utrecht University. Interleukin-2, a cytokine and immunostimulant, was combined

with marginal surgery in a pilot study of 17 dogs with MPNST and is currently tested in a double-blind prospective study. The initial results from the pilot study are encouraging. A pilot study in 17 dogs showed a recurrence free percentage at two years of approximately 70%.

Photodynamic therapy

Photodynamic therapy was used after surgery in dogs with HPC and appeared to have no advantage over other forms of therapy in regards to preventing recurrence. Complications, including delayed wound healing and infection, and limited efficacy decrease the applicability of this therapy type in dogs with STS.

REFERENCE

Kirpensteijn J, Rutteman GR, BSAVA Manual 2003