SOFT TISSUE SARCOMAS – WHAT’S NEW AND WHAT’S TRUE?

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Soft tissue sarcoma (STS) is a catch-all classification referring to tumours that arise from the embryonic mesoderm and as such can occur anywhere in the body. Generally they are classified according to cellular lineages (morphology on H and E staining, or immunohistochemistry (IHC)) such as fibrosarcoma, peripheral nerve sheath tumour, myxosarcoma, liposarcoma, or leiomyosarcoma, but sometimes these distinctions are not clear and the generic term soft tissue sarcoma or spindle cell sarcoma are employed. Some tumours of mesoderm behave in a much more aggressive and less predictable fashion and these tend not to be included in STS, examples include lymphangiosarcoma, rhabdomyosarcoma, synovial cell sarcoma, haemangiosarcoma, chondrosarcoma, osteosarcoma. Surgical resection is the principal treatment for primary localised disease as STS are relatively chemo-insensitive and radiotherapy is more of value in a curative context as an adjunct to surgery. The great variation in anatomic location, factored with variable size and grade, can present significant problems when making a treatment plan.

STS are graded into low (I), intermediate (II) and high (III) grade tumours taking into account histological features such as mitotic rate, extent of necrosis and cellular differentiation.

Radiographs may yield some information regarding local behaviour, but may only confirm the mass is of soft tissue density. Ultrasound (esp Doppler) can be useful but cross sectional imaging (CT or MRI) is the imaging of choice and is typically supportive of the diagnosis. Whereas MRI is traditionally regarded as superior for soft tissue detail, CT (esp contrast CT) offers a fast, simple, and accurate solution for all but the most complex STS. It is cheaper, equally as useful as MRI, and it has the advantage that imaging the thorax for metastatic disease can easily be performed at the same time.

In terms of biopsy, fine needle aspirates have an important role in ruling out more likely subcutaneous differentials for example mast cell tumours, lipomas or inflammatory lesions, all of which exfoliate cells well. If lucky enough mesenchymal cells will be aspirated from a STS to make a diagnosis. If an aspirate of a SQ mass
fails to yield many cells on the slide, your index of suspicion for a STS should be raised, and prompt a core biopsy. Percutaneous core biopsies (e.g. Trucut) are the best technique for achieving a safe and accurate diagnosis and can easily be performed with local anaesthetic alone or with sedation in nervous patients. Trucut biopsies will reliably differentiate benign from malignant disease and in most cases will also give a good indication of grade. The simplicity and accuracy of core biopsy for STS means incisional biopsies are infrequently indicated and come with the added concerns of location and direction of scar, and tumour dissemination from post-incisional biopsy haematoma.

Surgical resection is the most effective treatment for STS. The aim of curative-intent surgery is to widely excise the primary tumour (dogma; 3cm and/or a fascial plane) and achieve negative histopathological margins. The requirement for a 3cm margin to maximize local control of STS was challenged by Banks and Straw in 2004. In a prospective study, 14 dogs with 15 subcutaneous STS were treated using a standardized protocol. A lateral surgical margin of > 10mm and a single fascial plane deep (or > 10mm of deep tissue) yielded a local disease control rate of 100% with a 93% one year disease-free interval. Banks’ research into what is ‘an appropriate margin for STS’ is relevant, given that these masses can arise more-or-less anywhere, there is a great variety of biological behaviours seen between the grades, and putting the advice of ‘widely excise the primary tumour’ into practice is much more complex than other malignancies with less anatomical variation (e.g. lung, thyroid, intestine, mammary). Radiation has a role if incomplete margins are found, if further surgery is declined, or if the mass is close to important unresectable structures.

This is a different situation in the distal limbs however (typically at/below the stifle, and at/below the elbow) where a wide surgical margin of skin is usually only achievable using free skin grafts or random flaps, and options such as amputation or marginal resection and radiation are considered. Both these options have drawbacks in terms of altered function, morbidity and cost. Whereas it is expected amputation to treat an extremity sarcoma will effect a cure, marginal or incomplete excision of a STS and adjunctive curative-intent (hypofractionated) radiation results in a local recurrence rate of 19-35%.

In both human and veterinary surgical oncology, accepted guidelines on treatment of solid tumours have been difficult to establish. A large stumbling block in creating guidelines on treatment of STS is the uncertainty over what to do with an incomplete surgical margin and its relevance on local recurrence and overall survival. The impact of leaving residual tumour cells in the wound bed of an excised STS is a many fold increase in the rate of local recurrence (Kuntz). Several studies have reported the results of adjunctive radiotherapy in the management of STS with surgically incomplete margins and its success has generally been measured by its ability to provide consistently long overall survival times. The effect on local tumour control however, has been variable, with recurrence rates ranging from 17-60%.

Retrospective investigation into the results of surgery alone (‘primary re-excision’) for the treatment of STS after incomplete resection studied 41 dogs that had undergone aggressive scar revision (attempted wide margins (1-3cm)/1 fascial plane deep) for incompletely excised STS. Complete margins were obtained after re-excision in 90% (37/41) of all the cases with mean margin widths of 2.7cm on the proximal portion of limbs and 1.4cm on the distal portion of limbs. Local tumour recurrence occurred in 15% (6/39) of the dogs at a median time to recurrence of 142 days.
Comparisons of the local control rates achieved with re-excision of the scar compared to radiation therapy of the scar suggest that the outcomes of surgery, when possible, may be equivalent to those achieved with adjunctive radiation therapy. In fact, when the costs and relative morbidity of radiation are factored in, an attempt at surgical excision alone may be a more desirable first line approach. The question then arises, what if the site of recurrence does not afford an extensive re-excision, or the owner declines further treatment after a tumour positive margin is confirmed?

Two recent studies have evaluated the local recurrence rate of canine STS of the distal limbs treated by marginal excision alone (wait-and-see).

- The first (Cavanaugh et al, 2007) followed 26 dogs with tumours of the distal antebrachium or pes, all of whom were determined to have tumour positive margins after marginal excision by a variety of surgeons, some planned, some unplanned. All grades of STS were represented and follow-up intervals were long (median, 781 days, minimum 594 days). The rate of local recurrence was 37% (10/27 tumours) with only 12% (3/26) of the dogs being euthanized for problems relating to local disease.
- The second study (Stefanello 2008) was a retrospective review of planned marginal excisions of low grade distal extremity soft tissue sarcomas by two experienced surgeons. Using this technique, 32% surgeries has clean margins, 34% were ‘clean but close’ and 34% incomplete/dirty margins. Recurrence rate for this study was 11%. Follow up ranged from 210-2202 days.

Both these studies challenge the dogma that local recurrence rate following incomplete resection of STS is high, common, inevitable or guaranteed, depending on your text source. As is the goal of any retrospective study, these two raise questions rather than provide answers. The question which needs to be answered now is not HOW MANY recur, but what can we do to predict WHICH are likely to recur. Ettinger and Scase have shown that AgNORs and possibly Ki67 could be used over and above grade to help predict overall survival in STS, and for a starter, this work needs to be repeated in the context of local recurrence with a similar population of dogs with similar wounds in terms of tumour burden.

**Future directions and treatments??**

It would be ideal to identify those at risk of local recurrence or metastasis BEFORE surgery based on imaging and better predicting biological behaviour. We could then tailor the dose of surgery and treatment accordingly taking into account the animal’s age, status and prognosis. If we follow human advances, then intra-arterial chemotherapy, interventional chemo-embolisation or isolated limb-perfusion (melphalan/TNFα) are also treatments that may be considered in the future.

The bigger picture here is that STS in humans are relatively uncommon, accounting for <1% of all cancers, with 8500 new cases being diagnosed a year in the US, and 13000 in the EU. Although relatively rare in the dog, STS are seen commonly in secondary and tertiary referral practices. Scope for translational (what would be called pre-clinical trials in the human setting) exists and is likely to benefit both parties.