INTRODUCTION

Soft tissue sarcoma is a term used to describe a number of different types of tumor of mesenchymal origin with similar histological features and biological behavior.[1-3] Preventing local recurrence of the tumor following surgical resection is the characteristic challenge in the management of STSs. Local recurrence of tumour can develop in between 17-75% of all patients, with recurrence consistently associated with reduced overall survival for the dog. Bostock and Dye (1980) were the first to describe high rates of recurrence following conservative surgical resection, with local recurrence developing in more than 60% of patients with high-grade tumours.[4] A subsequent study by Kuntz et al (1997) suggested good outcomes could be achieved with wide resection margins.[5] In that paper, narrow resection margins and a higher tumour grade were associated with poorer outcomes. These prognostic findings were subsequently confirmed by several other authors. Largely as a consequence of these studies, surgical resection margins of 3cm lateral margins and a deep fascial plane have been traditionally recommended for the management of soft tissue sarcoma.[1, 3]

Recent publications have challenged this advice, and would suggest successful outcomes could be achieved for some STS with smaller margins.[6, 7] However, caution is required before recalibrating surgical margin recommendations for sarcoma resection based on these recent studies. Considerable selection bias exists in these different study populations, with varying proportions of tumour grade included which is very influential on outcome.[8] For this reason, it is unsurprising that surgical outcomes are better in those studies with a higher proportion of low-grade tumours,[7, 9-11] compared to those studies with more high-grade tumours.[4, 5, 12]

There are currently no diagnostic tests that can reliably predict the amount of surgical margin required for a particular tumour, leading to a mismatch between treatment and disease: some dogs are overtreated for their disease, resulting in large wound reconstructions or amputation when smaller surgical margins would have been effective. Other dogs are undertreated, and inappropriately conservative resections may result in inadequate tumour control.

Treatment strategies need to take account the behavioural characteristics of each individual tumor. It remains a concern that unplanned resection of the STS - with the operating surgeon having performed no prior diagnostic investigations to alert them to the malignant potential of the mass – remain common. In recent studies by the author, a diagnosis of STS was obtained in less than 20% of cases prior to surgery, and fewer than 10% of patients were operated with the surgical margins recommended in most textbooks for this tumour type.[7, 11]

STS are a complex disease and many uncertainties surround their biology and best options for clinical management. Approximately one in five patients will die as a result of their disease, and complacency in their care may have a detrimental impact on patient outcome. This lecture attempts to highlight some of the many uncertainties about sarcoma management, and hopefully pose some questions for future study or resolution by collaborative study.

ARE WE ALL TALKING ABOUT THE SAME DISEASE?

There is a bias for lower-grade tumours to be managed in first opinion practice.[7, 11] In one study, the majority (66%) of tumors were classified as low grade, with just 27.1% intermediate and 6.3% high-grade lesions. This contrasts with 36% intermediate and 22% high grade tumours in a referral population.[5] This bias towards more low-grade tumors in first opinion practice is also supported by analysis of pathology submissions to a UK commercial laboratory during a 3-year period, during which time 87% of
canine soft tissue sarcomas were classified as low grade, with smaller numbers of intermediate (8%) and high grade (3%) tumors.

The impact of this bias is important, but is rarely acknowledged. However, I think we would agree that the prognosis and treatment strategy for a 2 cm well-circumscribed mobile STS would be very different to an 8 cm STS with a necrotic centre, which has suddenly developed.

**DIAGNOSIS**

Dogs can develop a variety of masses in the subcutaneous region, many of which are benign. Palpation alone will not distinguish an innocuous mass (e.g. lipoma) from a mass that requires a carefully planned surgical strategy (e.g. mast cell tumour, STS). Nevertheless, a clinician should note the size, location and general delineation of the mass from the surrounding tissues as these features may play an important role in surgical triage and planning once a diagnosis of STS is made (see later).

**Cytology**

For any subcutaneous mass, interrogation by fine needle aspiration and cytology should always be the default step before any further treatment decisions are made. When performed successfully, cytology can be highly reliable (97%) at determining a mass to be a malignant mesenchymal tumour, but the precise type of sarcoma may only be identified in about two-thirds of cases. False positive and false negative results are possible, so interpretation of the results in light of the clinical features is important.

When performing a fine needle aspirate, one feature that should alert the clinician to the likelihood of a mass being a STS is a limited cell-harvest. Most other subcutaneous masses that are encountered in the dog, both benign and malignant, usually readily release cells into a needle such that a discernable drop of material is deposited onto the slide prior to smearing. By comparison, the cell harvest with STS may be minimal.

**Biopsy**

When cytology of a mass is non-diagnostic or features of the clinical presentation cast doubt on the validity of the cytology finding, an incisional biopsy using a tru-cut or skin punch will allow for histological diagnosis.

If an incisional biopsy is to be taken from a STS, samples should be taken from the main bulk of the mass, avoiding obviously necrotic or liquefactive tissues. When obtaining the biopsy, ensure the wound will be within the planned surgical field, and do not penetrate the deep boundary of the mass.

**Imaging**

Metastatic spread at the time of surgery is probably very uncommon for most low-grade STS, but the true incidence is poorly documented. Metastasis is more likely to occur with high grade tumours, with extension to regional lymph nodes also possible.

The use of coaxial imaging can assist with surgical planning in STS. Advanced imaging may not be required in every case, but can be invaluable for larger tumours (>4-5 cm in size) particularly if they are deeply positioned with ill-defined boundaries, or if they are located around a joint or other vital structures.

**TREATMENT**

Understanding the biology and growth characteristics of a STS is important when discussing treatment strategies. Surgery is currently the mainstay for the treatment of canine soft-tissue sarcomas. The goal of surgery must be to remove the gross tumour and the microscopic satellites that are in the surrounding reactive zone. Inadequate resection of the tumour will increase the likelihood for recurrence.

In general, the more ‘normal’ tissue that can be removed around a STS, the more likely it is that a curative outcome will be assured.Margins of between 2-3 cm are effective for the majority of STS. In most instances, it is better to err on the side of caution, rather than risk an incomplete resection. However, this assumes that good surgical technique has been followed.

**SURGICAL STRATEGIES FOR STS**
**En-bloc resection**
Conventional surgical technique for sarcoma resection involves measuring the desired surgical margin about the tumour and then maintaining a dissection plane about the entire circumference of the tumour from the skin, subcutaneous tissues, and muscles until an appropriate deep margin is penetrated. Muscles, nerves or blood vessels that branch into the resection field are cut at the measured border of the surgical margin. Only when the planned deep margin has been penetrated around the entire circumference of the surgical field should the dissection turn inwards from the measured margin, allowing the ‘block’ of tissue elevated from the wound – much like a pastry cutter removing a section of batter in a single unit.

With en bloc resection, it is presumed that if satellite nodules are present, they will be contained within the resected block of tissue. Because this extent cannot be reliably predicted for each individual tumour, prescribing wide surgical margins for all tumours has become the standard of care to reduce the risk of tumour recurrence.

**Compartmentectomy**
Very occasionally, a STS will arise within an individual muscle or muscle group. In those cases, removal of the whole “compartment” of tissue (e.g. a single muscle or a group of muscles surrounding a central tumor, removed from origin to insertion) may provide a superior outcome, both in terms of local tumour control and post-operative pain. Compartmentectomy ensures the tumour is surrounded by robust anatomic barriers on all sides, with the reactive zone and any satellite nodules contained within an entire natural compartment, rather than an arbitrarily-measured bloc of tissue.

**ADJUVANT TREATMENTS**
As a sole therapy for grossly visible disease, radiotherapy and/or chemotherapy are generally ineffective in the treatment of STS. However, both modalities have potential roles in either the neo-adjuvant or adjuvant setting to either slow or prevent local tumour recurrence or metastasis, or to improve the success of a planned surgical therapy.

**Radiotherapy**
Comparative experience from human STS would suggest that adjuvant radiotherapy could be important for the control of intermediate and high grade tumors in the dog. Incorporation of RT into a treatment strategy needs to be planned, and not simply relied upon to rescue a failed surgical resection. This requires close communication between the surgeon and radiation therapist, to ensure surgical boundaries are accurately documented to ensure the treatment field is appropriate. Photographs of the tumour prior to surgery, and also of the wound bed following resection, can be helpful to allow the radiotherapist to plan therapy. Further veterinary studies are required to enable better understanding of which patients are most likely to benefit from RT.

Several veterinary studies have demonstrated good efficacy for curative intent RT with daily fractions and a total dose above 50Gy. In a prospective veterinary study, intentional marginal excision was performed prior to four weekly doses of RT (8-9 Gy per dose) and a total treatment dose of 32-36G. Reasonable control was achieved with local tumour recurrence developing in 10/56 (18%) dogs, and a 1-, 3- and 5-year estimated recurrence rates of 19, 30 and 35% respectively. However, no control population was available so the true impact of therapy on tumour recurrence rate is unknown.

Radiation can also be used as a sole therapy for STS if the tumour is unresectable, or the surgical impact would be intolerable. Both curative-intent and palliative regimes have been shown to provide reasonable periods of tumour control (6-12 months), with better effects noted for higher total doses of radiation (>50Gy) and smaller tumours.

**Chemotherapy**
The role of chemotherapy in STS is unclear, with most human and veterinary studies failing to demonstrate an obvious survival advantage. However, this may be due to the very heterogeneous nature of the disease with any benefit for some tumour subtypes being masked by a poor response in others.
Currently, it is recommended for higher grade tumours only, but may still be appropriate for other larger tumours based on individual circumstance. Doxorubicin remains the most appropriate cytotoxic agent to use.

‘Continuous-low-dose’ (metronomic) chemotherapy is considered to slow progression by modulating the immunotolerance of the body to the tumour, and disrupting development of the vascular supply that is supporting the tumour. Metronomic chemotherapy has been proposed to offer some benefits over conventional chemotherapy, but clinical data is very limited. In one study, treatment with metronomic chemotherapy significantly prolonged the disease-free interval in dogs with incompletely resected soft tissue sarcoma compared to a population of historical controls. However, aspects of the study design make understanding the true benefit of treatment difficult to assess and further clinical studies are required.

There is a theoretical argument for using chemotherapy to try and downstage disease prior to surgery (i.e. neoadjunctively), particularly if optimal surgical margins are not available. Because it is delivered prior to surgery, the vascular supply of the tumour has not been disturbed, which should improve the prospects of drug penetration. The rationale for neoadjuvant chemotherapy is to kill off microscopic clusters of cells in the most biologically active regions of the tumour - essentially “sterilising” the reactive zone prior to surgical resection. However, there is currently limited data in the veterinary and human literature to support this strategy.

PROGNOSIS
The prognosis for the majority of cats and dogs with STS is generally good, provided a complete resection has been achieved. However, local recurrence can develop in up to 30% of dogs. Rates of metastasis are less well-defined, but may also develop in between 30-40% of cases. Overall, about 20-30% of dogs will ultimately die of their disease. Continued efforts to improve management options and to recognize those dogs with ‘bad disease’ remains important.

References