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Summary of **'Soft Tissue Sarcoma in the Dog – Part 1: A Current Review - J. P. Bray.**

Abstract

Soft tissue sarcomas originate from mesenchymal tissues. While the principal difficulty in managing these tumours is achieving durable local control after surgical excision, metastatic spread also represents a clinically significant concern. Approximately forty percent of dogs diagnosed with high-grade soft tissue sarcomas may ultimately develop metastatic disease, even when local tumour control appears successful. The biological behaviour of these tumours is heterogeneous, and many aspects of their pathogenesis and optimal clinical management remain uncertain. At present, no diagnostic modality is able to accurately predict the extent of surgical margins required for an individual tumour, which can result in a mismatch between treatment intensity and the true biological aggressiveness of the disease. Historically, wide surgical margins have been routinely advocated; however, emerging evidence suggests that such an approach may not always be justified. Apparent success with narrow excision margins in primary care settings is likely influenced by selection bias, with less aggressive tumours being over-represented. Conversely, insufficiently aggressive treatment strategies may compromise outcomes in dogs with biologically aggressive disease. This review presents an updated synthesis of current knowledge relating to the management of canine soft tissue sarcomas.

INTRODUCTION

Soft tissue sarcomas (STS) are neoplasms that arise from tissues of mesenchymal origin (Bostock & Dye 1980, Dernell et al. 1998, Ehrhart 2005, Mayer & Larue 2005). As mesenchymal tissues are widely distributed throughout the body, these tumours may develop at almost any anatomical location. In dogs, STS most commonly occur within subcutaneous tissues and represent a substantial proportion of neoplastic disease, accounting for approximately nine to fifteen percent of all cutaneous and subcutaneous tumours (Ehrhart 2005, Dennis et al. 2011, Liptak & Forrest 2013).

Failure of treatment in dogs with STS most frequently results from local tumour recurrence following surgical excision. Reported recurrence rates vary widely, ranging from seven to seventy-five percent, and recurrence is consistently associated with a reduction in overall survival (Bostock & Dye 1980, Kuntz et al. 1997, Banks et al. 2004, Ehrhart 2005, Heller et al. 2005, Liptak & Forrest 2013, Bray et al. 2014a).

Several publications indicate that outcomes for dogs with STS have improved over the past three decades (Bostock & Dye 1980, Stefanello et al. 2008, Chase et al. 2009, Bray et al.

2014a). These improvements may reflect earlier detection, improved case selection, and reporting bias associated with populations treated in either primary care or referral institutions (Bray et al. 2014a). Despite this apparent progress, unplanned tumour resections—defined as excisions performed without prior diagnostic assessment to establish malignant potential—remain common in veterinary practice (Chase et al. 2009, Bray et al. 2014a).

Although overall outcomes may appear favourable, approximately twenty percent of dogs with STS will ultimately succumb to their disease. A lack of vigilance or inappropriate conservatism in clinical decision-making may therefore have a detrimental effect on patient survival. The purpose of this review is to summarise contemporary understanding of the management of canine soft tissue sarcomas and to outline emerging directions in treatment. A subsequent review will explore current controversies in greater depth and assess relevant findings from the human medical literature that may inform future advances in veterinary management.

NOMENCLATURE AND BIOLOGICAL BEHAVIOUR

A wide range of soft tissues originate from the embryonic mesoderm, including skeletal and smooth muscle, tendons, ligaments, joint capsules, fascia, peripheral nerves, and both blood and lymphatic vessels (Dennis et al. 2011, Liptak & Forrest 2013). Although neoplasms may arise from any of these tissues, not all mesenchymal tumours are classified as soft tissue sarcomas (Dennis et al. 2011). Certain tumours are excluded from the STS category because they can usually be identified reliably using light microscopy—particularly when their anatomical location is known—and because their biological behaviour is more consistently defined (Dennis et al. 2011).

Mesenchymal tumours typically excluded from the STS grouping include haemangiosarcoma, synovial cell sarcoma, gastrointestinal stromal tumours, fibrosarcomas arising within the oral cavity, and peripheral nerve sheath tumours originating from the brachial or lumbosacral plexus. There remains some disagreement regarding the classification of rhabdomyosarcoma, lymphangiosarcoma, and leiomyosarcoma; while some pathologists include these tumours within the STS category, others prefer to exclude them (Ehrhart 2005, Dennis et al. 2011, Liptak & Forrest 2013).

Soft tissue sarcomas have traditionally been grouped together due to shared characteristics of biological behaviour that are broadly consistent across tumour types (Liptak & Forrest 2013). These defining features, originally described by Withrow and MacEwan, include the ability to arise at almost any anatomical site, the tendency to form pseudo-encapsulated masses with poorly defined microscopic margins, infiltration along fascial planes, frequent local recurrence following conservative surgical excision, haematogenous metastatic spread,

and a generally poor response to chemotherapy and radiotherapy when gross disease remains present.

Although individual STS may demonstrate distinct histological features, they are commonly classified as a single group because of their similar biological behaviour and the difficulty of reliably differentiating them using light microscopy alone (Dennis et al. 2011, Liptak & Forrest 2013). Some pathologists have proposed the term “spindle cell tumour of canine soft tissue” to describe a subset of these tumours that typically exhibit lower-grade biological behaviour (Williamson & Middleton 1998, McSporran 2009, Liptak & Forrest 2013).

Tumour types generally included within the STS classification encompass fibrosarcoma, perivascular wall tumours (formerly termed haemangiopericytoma), liposarcoma, malignant fibrous histiocytoma, mesenchymoma, myxosarcoma, non-plexus-derived peripheral nerve sheath tumours (previously referred to as neurofibrosarcoma or schwannoma), and undifferentiated sarcoma.

The metastatic behaviour of canine STS remains incompletely characterised. These tumours are commonly described as having a low to moderate propensity for metastasis, although the supporting data are limited. Reported metastatic rates range widely, from as low as 1.7 percent to as high as 41 percent (Bostock & Dye 1980, Kuntz et al. 1997, Heller et al. 2005, Stefanello et al. 2011, Demetriou et al. 2012). Much of this variability likely reflects differences in study design and the intensity of diagnostic investigation. Increased metastatic risk has been associated with higher histological grade and increased mitotic activity (Dennis et al. 2011). When metastasis does occur, the lungs represent the most frequent site, whereas involvement of regional lymph nodes is relatively uncommon (Kuntz et al. 1997).

CAUSES

Isolated case reports have documented the development of soft tissue sarcomas in dogs in association with a range of antecedent events, including prior traumatic injury, parasitic infection such as *Spirocerca lupi*, implanted foreign materials, and surgical trauma (Vascellari et al. 2003, 2006, van der Merwe et al. 2008, Rayner et al. 2010). Neoplastic transformation associated with vaccination, injectable materials, or retained foreign bodies has also been reported in cats and humans (Hendrick & Goldschmidt 1991, Seguin 2002, Moizhess 2008, Haddad et al. 2010, Carminato et al. 2011, Martano et al. 2011). Despite these associations, the aetiology of sarcoma development in the dog remains largely unknown in the majority of cases.

Insights from human oncology indicate that the molecular genetics underlying soft tissue sarcomas are highly complex and disorganised. Molecular classification systems divide sarcomas into two principal categories. The first group includes tumours characterised by

specific genetic alterations, such as distinct chromosomal translocations or identifiable oncogenic mutations. The second group comprises tumours with complex genomic profiles, often containing dozens of molecular abnormalities (Bovee & Hogendoorn 2010, Teicher 2012). Most soft tissue sarcomas fall into this latter category, suggesting that a single, common mutational pathway is unlikely to underlie tumour initiation.

The absence of a consistent genetic signature implies that tumour development and progression may occur as stochastic events. This process may be facilitated or exacerbated by increased mutational activity within regions of chronic or localised inflammation (Radons 2014a, 2014b). Such inflammatory microenvironments may promote genomic instability, thereby increasing the likelihood of malignant transformation in susceptible mesenchymal tissues.

CLINICAL FEATURES

Epidemiological data from the United Kingdom indicate that soft tissue sarcomas have one of the highest reported tumour incidence rates in dogs. Analysis of insurance records estimated an incidence of 122 cases per 100,000 dogs per year, with a ninety-five percent confidence interval ranging from 103 to 141 (Dobson et al. 2002). Comparable findings have been reported elsewhere; for example, a study from the Netherlands examining tumour prevalence in golden retrievers estimated an annual incidence rate of 114 STS cases per 100,000 dogs (Boerkamp et al. 2014).

No consistent breed predisposition has been identified for the development of STS. However, dogs of medium to large body size appear to be more frequently affected (Dernell et al. 1998, Ehrhart 2005, Mayer & Larue 2005, Liptak & Forrest 2013). Reported sex distribution varies between studies, but neither sex nor neuter status appears to influence tumour development or disease progression. Affected dogs are typically middle-aged to older, with median ages at diagnosis reported between ten and eleven years, although cases have been documented in dogs as young as two years and as old as sixteen years (Ehrhart 2005, Stefanello et al. 2008, Chase et al. 2009, Dennis et al. 2011, Liptak & Forrest 2013, Bray et al. 2014a).

Most dogs with STS present with a palpable subcutaneous mass (Ehrhart 2005, Liptak & Forrest 2013). In many cases, owners report that the mass has been present for several months, although some tumours may enlarge rapidly before stabilising in size. While STS are generally regarded as slow-growing neoplasms, it is not uncommon for a large mass to be identified shortly after initial detection by the owner. In other cases, veterinary assessment is prompted by a recent change in the size, consistency, or appearance of a previously noted mass. Very large tumours may ulcerate if growth outpaces the capacity of the overlying skin or if areas of the tumour undergo necrosis (Liptak & Forrest 2013). Such cases may be

accompanied by local inflammation and discharge of necrotic material, and in severe circumstances the associated morbidity may necessitate consideration of limb amputation or euthanasia.

On physical examination, STS typically appear as firm, well-filled masses that expand beneath the skin. The majority of tumours—up to sixty percent—are located on the limbs (Banks et al. 2004, Ehrhart 2005, Liptak & Forrest 2013, Bray et al. 2014a). Approximately thirty-five percent occur on the trunk, including the tail, while around five percent are found on the head. These tumours are usually non-painful. Palpation may reveal that the mass is firmly attached to underlying tissues, although in some cases it may be freely mobile and appear to "wobble" beneath the skin (Chase et al. 2009, Liptak & Forrest 2013).

Clinical signs beyond the presence of a mass are uncommon and are largely determined by tumour location. When STS are situated deep within tissues or closely associated with joints, lameness may be the only presenting complaint, and the mass itself may not be readily detectable during routine physical examination (Bray et al. 2014b). Although metastasis to regional lymph nodes is considered infrequent (Kuntz et al. 1997), thorough palpation and cytological evaluation of draining lymph nodes is recommended as part of the initial clinical assessment (Dennis et al. 2011).

DIAGNOSIS

A presumptive diagnosis of soft tissue sarcoma can often be supported through cytological evaluation of samples obtained by fine needle aspiration (Dernell et al. 1998, Stockhaus et al. 2003, Ehrhart 2005, Dennis et al. 2011, Liptak & Forrest 2013). However, careful attention must be paid to both sample acquisition and interpretation. Mesenchymal cells typically exfoliate poorly, and reactive or inflammatory tissue can exhibit cytological features that closely resemble those of neoplasia. As a result, provision of a detailed clinical history and a thorough description of the mass are essential to assist the pathologist in contextualising the cytological findings (Kamstock et al. 2011).

In one study, cytology enabled classification of subcutaneous masses as neoplastic with a sensitivity of 89.3 percent and a specificity of 97.9 percent. The positive predictive value was 99.4 percent, while the negative predictive value was 68.7 percent (Ghisleni et al. 2006). A diagnosis of malignant mesenchymal tumour was achieved in 97.1 percent of cases; however, cytomorphological features were often insufficiently distinctive to permit accurate identification of a specific STS subtype. Consequently, a non-specific diagnosis of sarcoma was rendered in 67.2 percent of cases. An exception was noted for perivascular wall tumours, for which cytology enabled correct identification in 96 percent of cases (Ghisleni et al. 2006).

Cytological evaluation does not provide information regarding tumour grade or other histological characteristics relevant to biological behaviour and treatment planning (Stockhaus et al. 2003). Such information can only be obtained reliably through histopathological examination of tissue samples.

Histological grading is the most important prognostic indicator in human soft tissue sarcoma and is likely among the most robust predictors of outcome following surgery in dogs (Kuntz et al. 1997, McSporran 2009, Bray et al. 2014a). For this reason, pre-operative biopsy to determine tumour type and grade is strongly recommended, particularly when planned surgery carries the risk of functional impairment. Incisional biopsies may be obtained using a scalpel, biopsy punches, needle-core biopsy devices, or trephines (Ehrhart 1998, Ettinger 2003, Ehrhart & Withrow 2007).

For canine STS, percutaneous needle-core biopsy instruments, typically 12- to 14-gauge devices such as Tru-cut needles or trephines, are particularly effective. These instruments may be inserted using direct palpation or under ultrasound guidance. Biopsy procedures may be performed under local anaesthesia or with sedation or general anaesthesia, depending on tumour location and patient temperament (Ehrhart & Withrow 2007). Because needle-core biopsies sample only small portions of the tumour, multiple cores should be collected from different regions to improve diagnostic accuracy; a minimum of six cores is recommended when using Tru-cut needles.

Tumour cell implantation along the biopsy tract represents a recognised complication of percutaneous biopsy (Robertson & Baxter 2011). In human oncology, the reported incidence of biopsy tract seeding varies depending on tumour type, ranging from less than one percent for bone and soft tissue tumours to as high as twenty-two percent for mesothelioma. The clinical impact of this complication can be mitigated by ensuring that biopsy tracts are positioned such that they can be fully excised during definitive surgery, and by avoiding disruption of fascial planes surrounding the tumour.

Evidence from human soft tissue sarcoma studies indicates that needle-core biopsy provides diagnostic accuracy comparable to that of open biopsy, correctly distinguishing between high- and low-grade tumours in approximately ninety-three percent of cases (Ball et al. 1990, Heslin et al. 1997). In dogs, one study reported that pretreatment biopsies underestimated the final histological grade in twenty-nine percent of cases and overestimated it in twelve percent when compared with the grade assigned after tumour resection (Perry et al. 2014). These findings suggest that while pretreatment biopsy is generally reliable for differentiating high- from low-grade sarcomas, a diagnosis of low-grade disease should be interpreted cautiously.

Given the potential importance of histological grade in determining the appropriate extent of surgical intervention (McSporran 2009), these limitations underscore the need for more objective and reliable prognostic markers in both canine and human soft tissue sarcoma (Pisters et al. 1996, Yudoh et al. 2001, Gustafson et al. 2003, Zagars et al. 2003b, Engellau et al. 2005, Matsumine et al. 2007, Kilvaer et al. 2010, Dennis et al. 2011, Sampo et al. 2012, Kondo et al. 2013).

TREATMENT PLANNING

A large retrospective analysis demonstrated that more than eighty percent of soft tissue sarcoma excisions performed in primary care settings were undertaken without prior diagnostic planning. In these cases, the surgeon had no definitive information regarding the tumour's histological identity, biological behaviour, or invasive potential at the time of removal (Bray et al. 2014a). The predominance of low-grade, less aggressive sarcomas encountered in first-opinion practice likely offsets this lack of planning and contributes to the generally acceptable outcomes reported in such populations (Bray et al. 2014a).

In contrast, data from human oncology—where higher-grade sarcomas are more prevalent—demonstrate that incomplete excision resulting from unplanned surgery is consistently associated with reduced overall survival. This negative impact persists even when additional surgery or adjuvant radiotherapy is subsequently performed (Gustafson et al. 1994, Chen et al. 2011, Qureshi et al. 2012). Comparable large-scale veterinary studies are lacking. One veterinary report described apparently favourable outcomes following re-excision of recently and inadequately removed canine STS; however, the absence of a control population limits interpretation of these results (Bacon et al. 2007).

Adjuvant radiotherapy following incomplete excision of STS has been associated with one- and three-year survival rates ranging from eighty to eighty-seven percent and sixty-one to eighty-one percent, respectively. Median times to local recurrence of approximately 698 days and greater than 798 days have been reported (Forrest et al. 2000, McKnight et al. 2000, Kung et al. 2014). Despite these results, reoperation or radiotherapy may not be feasible for all patients or owners, highlighting the importance of thorough pre-operative assessment and planning when managing a potentially malignant mass.

At present, no diagnostic test can reliably define the precise surgical margins required for an individual STS. Nevertheless, several prognostic factors have been validated or proposed (Dennis et al. 2011). These include histological variables such as tumour grade, histological subtype, and mitotic count; physical characteristics such as tumour size, anatomical location, and palpation findings; and patient-related factors including age and concurrent disease. After tumour removal, assessment of surgical margin completeness is also a critical

prognostic element and should be interpreted within the broader context of the treatment plan.

Histologic assessment

Histologic type

For prognostic purposes, canine soft tissue sarcomas have traditionally been treated as a single disease entity (Dennis et al. 2011). In human oncology, increasing evidence suggests that individual sarcoma subtypes differ in their tendencies for local invasion, recurrence, and metastatic spread (Canter et al. 2010, Tseng et al. 2012). In dogs, however, evidence supporting outcome differences between specific histological subtypes is limited, largely due to small study populations or inconsistent diagnostic criteria.

In one large retrospective veterinary study in which tumour histology was reviewed by a single board-certified pathologist, differences in local recurrence rates were identified between subtypes. Higher recurrence rates were observed for neurofibrosarcoma (32.1 percent), myxoma (30.7 percent), and fibrosarcoma (28.6 percent), whereas perivascular wall tumours demonstrated a substantially lower recurrence rate of nine percent (Bray et al. 2014a). Similar trends have been described by other authors (Dennis et al. 2011), and some have proposed that perivascular wall tumours represent a relatively indolent subtype within the STS spectrum (Avallone et al. 2007, Stefanello et al. 2011).

Accurate distinction between STS subtypes—and between biologically aggressive and less aggressive forms—remains challenging. This limitation may adversely influence outcomes, particularly in clinical settings where single-modality treatment is commonly employed (Dennis et al. 2011). Until these uncertainties are resolved, clinicians should recognise that a continuum of biological aggressiveness exists within the STS group, even though the implications for prognosis and treatment selection are not yet fully defined.

Grade

Tumour grade is assigned as low (Grade I), intermediate (Grade II), or high (Grade III) based on a combination of histological parameters, including degree of differentiation, mitotic activity, and the extent of tumour necrosis, as outlined in established grading systems (Dennis et al. 2011). Increasing tumour grade is strongly associated with more aggressive biological behaviour, manifesting as higher rates of local recurrence, increased metastatic

risk, and shorter disease-free intervals (Kuntz et al. 1997, McSporran 2009, Dennis et al. 2011).

Low-grade sarcomas constitute the majority of cases encountered in veterinary practice, although reported prevalences are influenced by the source of tumour samples. Studies based on cases from primary care practices report predominance of low-grade tumours, comprising between fifty-one and eighty-four percent of cases, with high-grade tumours representing only 6.3 to seven percent (McSporran 2009, Bray et al. 2014a). In contrast, referral-based studies demonstrate a substantially higher proportion of high-grade tumours, ranging from 22.7 to twenty-nine percent (Kuntz et al. 1997, Heller et al. 2005).

Mitotic index and proliferative markers

Mitotic index, defined as the number of mitotic figures identified per ten high-power microscopic fields, provides an estimate of tumour proliferative activity and offers additional prognostic information (Dennis et al. 2011). Elevated mitotic indices have been correlated with increased likelihood of tumour recurrence, earlier metastatic spread, and reduced overall survival (Bostock & Dye 1980, Kuntz et al. 1997, Ettinger et al. 2006, McSporran 2009, Dennis et al. 2011, Bray et al. 2014a).

Other proliferative markers, including argyrophilic nucleolar organising regions (AgNOR) and Ki-67, assess proliferative activity across the entire mitotic cycle rather than capturing a single time point, as is the case with mitotic index (Ettinger et al. 2006). Increased expression of these markers has been associated with shorter survival times and correlates with other indicators of aggressive tumour behaviour, such as higher grade and increased mitotic activity. Despite their prognostic value, these markers have not been routinely incorporated into standard evaluation of canine STS.

Tumour size and growth rate

From a surgical perspective, larger tumours are generally considered more difficult to excise completely than smaller lesions (Azzarelli 1993). Several studies in both canine and human patients have reported that tumours exceeding five centimetres in diameter are associated with shorter disease-free intervals and reduced survival (Mandard et al. 1989, Guillou et al. 1997, Kuntz et al. 1997, Stojadinovic et al. 2002, Gustafson et al. 2003, Monteiro et al. 2011, Sampo et al. 2012, Bray et al. 2014a). Other investigations, however, have failed to demonstrate a significant association between tumour size and outcome (Bostock & Dye 1980, Bacon et al. 2007, Chase et al. 2009).

Although not formally validated, a clinical history of rapid tumour enlargement, sudden growth acceleration, or the presence of ulceration or necrosis may suggest more aggressive biological behaviour and should prompt cautious treatment planning (Liptak & Forrest 2013).

Palpable characteristics

Most soft tissue sarcomas are readily detectable on palpation and may appear discrete and superficially encapsulated. In contrast, some tumours exhibit a multilobulated, soft consistency with poorly defined margins. While superficial portions of the mass may appear mobile, the deep aspect may be indistinct or firmly attached to underlying fascia or bone (Liptak & Forrest 2013).

Tumour mobility may carry prognostic significance. Tumours that are palpably fixed to underlying tissues have been associated with significantly shorter disease-free intervals and survival times (Bray et al. 2014a). One proposed explanation is that such tumours possess a microenvironment that promotes local infiltration or facilitates peripheral tumour cell migration (Barker et al. 2012). Other studies, however, have not confirmed tumour fixation as a reliable prognostic indicator (Dennis et al. 2011), and prospective investigation is required to clarify its value in predicting surgical margins.

Imaging

Diagnostic imaging fulfils two primary roles in the management of soft tissue sarcomas: oncological staging and surgical planning.

Staging

Thoracic imaging, using three- or four-view radiographs or computed tomography, should be considered in all cases to evaluate for pulmonary metastasis (Ehrhart 2005), although detectable metastases at the time of surgery are relatively uncommon. Abdominal ultrasonography generally yields a low diagnostic return in STS but may be appropriate for tumours of higher histological grade.

Planning

On computed tomography or magnetic resonance imaging, fascia appears relatively radiodense due to its high collagen content, allowing clear delineation of tissue planes (LeBlanc & Daniel 2007). Administration of contrast agents can further enhance

discrimination between tumour tissue and adjacent structures. Advanced imaging enables assessment of whether the tumour is confined within well-defined anatomical compartments or has extended beyond these boundaries into poorly defined fascial planes (Hahn et al. 1990, Kraun et al. 2015). Magnetic resonance imaging may offer superior soft tissue contrast compared with computed tomography, although direct comparative studies in dogs are lacking (LeBlanc & Daniel 2007).

Margin evaluation

Achieving histologically tumour-free surgical margins is consistently associated with prolonged tumour-free intervals and improved survival (Stojadinovic et al. 2002, Banks et al. 2004, Dickinson et al. 2006, Chase et al. 2009, Dennis et al. 2011, Nurkin & Kane III 2012, Qureshi et al. 2012, Scarpa et al. 2012). For this reason, submission of the entire excised tumour for histopathological evaluation is essential.

Given inherent limitations in margin assessment, responsibility lies with the surgeon to ensure that submitted specimens accurately represent the surgical field. The surgeon is best positioned to identify margins of concern or areas compromised by anatomical constraints. Such regions should be clearly marked with sutures and specifically highlighted for the pathologist. Application of coloured inks to lateral and deep margins can further aid accurate margin identification, particularly when tissue distortion occurs during fixation (Kamstock et al. 2011).

An additional technique to improve margin assessment involves sampling tissue from the wound bed following tumour excision, commonly referred to as shave margins. These samples are analysed separately to detect residual tumour cells. In human oncology, intraoperative evaluation of shave margins has been shown to reduce rates of positive margins (Harness et al. 2014). In veterinary patients, shave margins identified residual tumour cells not detected in the main specimen in 4.9 percent of cases and suggested possible false-positive main margin assessments in 9.8 percent (Harris et al. 2014).

TREATMENT

Surgery

Within veterinary medicine, surgical excision remains the cornerstone of treatment for soft tissue sarcomas. Nevertheless, there is ongoing debate regarding the optimal manner in which surgery should be applied (Angelov et al. 1999, Banks et al. 2004, Cavanaugh et al. 2007, Stefanello et al. 2008, Prpich et al. 2013, Bray et al. 2014a). A companion review

addresses controversies surrounding surgical margins in greater detail, and readers are encouraged to consider both articles when formulating treatment strategies for canine STS.

Traditionally, surgical guidelines for STS have recommended wide local excision, involving en bloc removal of the tumour with at least three centimetres of macroscopically normal tissue circumferentially and inclusion of one intact fascial plane deep to the tumour (Kuntz et al. 1997, Dernell et al. 1998, Ehrhart 2005, Liptak & Forrest 2013). More recent studies have questioned the necessity of such extensive margins (Banks et al. 2004, Cavanaugh et al. 2007, Chase et al. 2009, Bray et al. 2014a), with several reports suggesting that margin width may not significantly influence disease-free interval or overall survival (Stefanello et al. 2008, Chase et al. 2009, McSporran 2009, Bray et al. 2014a).

Despite these findings, caution is warranted before revising established surgical margin recommendations. Many of the studies advocating narrower margins include substantial selection bias, particularly with respect to tumour grade. McSporran (2009) demonstrated that tumour grade exerted a marked influence on recurrence risk: only seven percent of low-grade tumours recurred following marginal excision, compared with thirty-four percent of intermediate-grade tumours and seventy-five percent of high-grade tumours. Consequently, favourable outcomes reported in studies with a high proportion of low-grade tumours (Stefanello et al. 2008, Chase et al. 2009, Bray et al. 2014a) are not directly comparable with studies that included a greater number of high-grade lesions (Bostock & Dye 1980, Kuntz et al. 1997, Banks et al. 2004, Heller et al. 2005).

At present, no diagnostic modality can reliably determine the optimal surgical margins required for an individual sarcoma (Banks et al. 2004, Stefanello et al. 2008, Chase et al. 2009, McSporran 2009, Bray et al. 2014a). Until such tools are available, margins of two to three centimetres laterally and inclusion of one deep fascial plane should continue to be regarded as an appropriate target when surgery is employed as the sole treatment modality (Kuntz et al. 1997, Banks et al. 2004, Kawaguchi et al. 2004, Dickinson et al. 2006, Cavanaugh et al. 2007, Prpich et al. 2013, Bray et al. 2014a).

This approach may result in overtreatment for some patients; however, excessively conservative excision is likely to compromise outcomes in dogs with biologically aggressive disease. In selected cases, strategic reduction of surgical margins may be considered based on individual prognostic features, but the limitations of existing evidence must be acknowledged. In all cases, the entire excised tumour should be submitted for histopathological assessment, including grading and margin evaluation (Kamstock et al. 2011).

Successful resection of large soft tissue sarcomas requires detailed anatomical knowledge, adherence to oncological surgical principles, advanced technical skills, and appropriate peri-

operative nursing care. Although lateral margins can be planned and marked prior to incision, maintaining these boundaries during dissection and identifying a reliable deep margin can be challenging, particularly for less experienced surgeons. Extensive resections are technically demanding (Prpich et al. 2013), and outcomes may vary according to surgical expertise. For example, Monteiro et al. (2011) reported a significantly higher risk of incomplete excision when tumours were removed by surgical residents compared with board-certified surgeons.

Similar disparities have been documented in human medicine, leading to recommendations that soft tissue sarcomas be managed by specialised surgeons within dedicated centres (Gustafson et al. 1994, Jansen-Landheer et al. 2009). While implementation of such systems may be challenging in veterinary practice, these findings underscore the complexity inherent in STS management, particularly for large or high-grade tumours.

Tumours arising on the distal limb present additional challenges. Surgical excision in these locations may compromise function if essential neurovascular or supportive structures are involved, and suitable deep fascial barriers are often limited. Reconstruction of resultant skin defects may also be required (Prpich et al. 2013). Some studies have suggested that incompletely excised distal limb tumours recur less frequently than those located on the trunk (Kuntz et al. 1997), although this observation has not been consistently replicated (Dennis et al. 2011). Analysis of a large cohort demonstrated no significant variation in tumour grade distribution between lesions originating on the head, trunk, or limbs (Bray et al. 2014a). The perception that distal limb tumours exhibit more favourable behaviour may therefore reflect referral bias, with specialists encountering a disproportionate number of low-grade cases.

Because vascularised flap options are limited for distal limb reconstruction, one study evaluated wide local excision of STS in this region followed by second intention wound healing (Prpich et al. 2013). Tumours were removed with two-centimetre lateral margins and inclusion of a deep fascial plane. All cases achieved histologically clean margins. Most tumours were classified as Grade I (77.4 percent), with the remainder being Grade II; no Grade III tumours were included. The median time to wound healing was fifty-three days, and excellent long-term limb function was reported. Local recurrence occurred in a single dog (3.2 percent) over a median follow-up period of 980 days.

In some cases, curative surgical excision with wide margins is not feasible. Anatomical constraints, patient comorbidities, financial limitations, or owner preferences may preclude extensive surgery. Given that many STS can be effectively managed with long-term local control, it is essential that treatment goals and expectations are clearly discussed before deviating from established guidelines. Prognostic information derived from incisional biopsy, such as tumour grade and mitotic index, along with physical tumour characteristics including

size and growth rate, may help identify cases where conservative excision is an acceptable compromise. However, as none of these features reliably predict individual outcomes (Cavanaugh et al. 2007, Dennis et al. 2011), consultation with or referral to a surgical oncologist should be strongly considered.

Multimodal treatment strategies incorporating adjuvant radiotherapy and or chemotherapy may permit reduction in surgical extent without increasing local recurrence risk. Evidence from human oncology suggests that such planned approaches yield superior outcomes compared with unplanned limited excision (Pisters et al. 1996, Miller et al. 2015).

Adjuvant therapy

Radiotherapy

In human oncology, radiotherapy is regarded as a central component of effective local treatment for soft tissue sarcomas. When combined with surgery, radiotherapy has allowed a reduction in surgical margins without compromising local control or survival, provided treatment is delivered within a carefully planned and coordinated framework (Rosenberg et al. 1982, Pisters et al. 1996, Zagars et al. 2003a, Miller et al. 2015). Modern series involving combined modality treatment typically report local tumour control rates exceeding eighty percent (Miller et al. 2015). Radiotherapy may be administered either before surgical excision (neoadjuvant) or following surgery (adjuvant). Available evidence indicates no clear difference in oncological outcome between these approaches, although the timing of radiation may influence the likelihood and severity of treatment-related complications such as impaired wound healing (Zagars & Ballo 2003, Zagars et al. 2003a, 2003b).

In veterinary patients, favourable outcomes have been reported following curative-intent radiotherapy after incomplete excision of soft tissue sarcomas. Forrest et al. (2000) described a median survival time of 2270 days in dogs with non-oral STS treated with postoperative radiotherapy, using total doses ranging from forty-two to fifty-seven gray delivered in daily fractions of three to 4.2 gray. McKnight et al. (2000) employed a total dose of sixty-three gray administered in three-gray fractions on alternate days, reporting a five-year survival rate of seventy-six percent and a median disease-free interval of 1082 days. In both studies, the development of metastasis and local tumour recurrence were significantly associated with reduced survival.

In these veterinary series, radiotherapy was introduced only after histologically incomplete margins had been identified following attempted surgical excision. In contrast, human studies demonstrate that unplanned positive margins resulting from surgical error are associated with poorer survival outcomes, even when adjuvant radiotherapy is applied with curative intent (Chen et al. 2011). However, patients undergoing planned marginal excision

to preserve limb function, followed by radiotherapy, achieve outcomes comparable to those with negative margins.

A more recent veterinary study evaluated the use of hypofractionated radiotherapy following intentionally marginal excision of limb STS (Demetriou et al. 2012). The protocol consisted of four weekly treatments delivering six to nine gray per fraction, to a total dose of twenty-four to thirty-six gray. Local recurrence rates ranged from eighteen to twenty-one percent, while metastatic disease developed in twenty-three to twenty-five percent of dogs, with follow-up periods between 240 and 2376 days. Incomplete margins were reported in the majority of cases. The absence of a control population limits assessment of treatment efficacy.

Due to tumour heterogeneity and selection bias across studies, definitive evaluation of radiotherapy protocols in veterinary STS will require well-designed prospective clinical trials. Further investigation is necessary to identify which patients are most likely to benefit from radiotherapy, and close collaboration between surgeons and radiation oncologists is essential to optimise therapeutic benefit while minimising adverse effects.

Chemotherapy

Although metastatic disease represents a major cause of mortality in humans with soft tissue sarcoma, the role of adjuvant systemic chemotherapy—most commonly doxorubicin-based—remains controversial. Meta-analyses have reported either no measurable benefit (Woll et al. 2012) or modest improvements in local recurrence, distant recurrence, and overall recurrence rates (Pervaiz et al. 2008). Consequently, adjuvant chemotherapy is not routinely employed in human STS management but is considered selectively for high-grade tumours or specific histological subtypes (Patrikidou et al. 2011).

In veterinary oncology, evidence supporting the use of chemotherapy for STS is limited. One study assessing adjuvant doxorubicin therapy in dogs with high-grade sarcomas failed to demonstrate a significant improvement in recurrence rates, metastatic development, or overall survival compared with dogs that did not receive adjuvant treatment (Selting et al. 2005).

Interest has increased in low-dose continuous, or metronomic, chemotherapy due to its potential to delay tumour recurrence in dogs with incompletely excised STS (Elmslie et al. 2008). Rather than exerting direct cytotoxic effects, this approach is believed to inhibit tumour progression through anti-angiogenic mechanisms and modulation of immune responses (Burton et al. 2011). In a comparative study involving treated dogs and untreated controls, significantly prolonged disease-free intervals were observed in dogs receiving

metronomic therapy (Elmslie et al. 2008). Interpretation of these findings is limited by potential selection bias, as all control dogs experienced tumour recurrence or were censored.

Neoadjuvant chemotherapy, defined as systemic treatment administered prior to surgical excision, is widely utilised in human oncology for various tumour types (Hohenberger & Wysocki 2008, Fujiki et al. 2011). Several prospective human studies suggest potential survival benefits for patients with high-grade STS treated with neoadjuvant chemotherapy, although results remain inconclusive (Gortzak et al. 2001, Wodajo et al. 2001, Lietman 2010). Proposed advantages include improved drug penetration into intact tumour vasculature and histological alteration of the tumour pseudocapsule. Experimental and clinical studies have demonstrated that neoadjuvant therapy may induce formation of a thickened, collagen-rich capsule devoid of viable tumour cells, thereby facilitating complete surgical excision (Gitelis et al. 1989, Wodajo et al. 2001). Comparable clinical studies have not yet been conducted in dogs, and the impact of neoadjuvant therapy on surgical margins or outcome in canine STS remains unknown.

PROGNOSIS

The overall prognosis for dogs with soft tissue sarcoma is generally favourable when complete surgical excision is achieved (Kuntz et al. 1997, McSporran 2009, Dennis et al. 2011, Bray et al. 2014a). However, local tumour recurrence remains common, particularly when surgical margins are incomplete, with reported recurrence rates of up to seventy-five percent (Bostock & Dye 1980, Kuntz et al. 1997, Baker-Gabb et al. 2003, Banks et al. 2004, Heller et al. 2005, Selting et al. 2005, Cavanaugh et al. 2007, Stefanello et al. 2008, Chase et al. 2009, Bray et al. 2014a).

The incidence of metastatic disease is less clearly defined but has been reported to range between 1.7 and forty-one percent (Kuntz et al. 1997, Banks et al. 2004, Dennis et al. 2011, Bray et al. 2014a). Overall, approximately twenty to thirty percent of dogs with STS will ultimately die as a result of their disease. Continued efforts to improve treatment strategies and to identify reliable prognostic indicators remain essential to optimise outcomes and to tailor therapy to the biological behaviour of individual tumours (Kuntz et al. 1997, Angelov et al. 1999, Heller et al. 2005, Selting et al. 2005, Bacon et al. 2007, Cavanaugh et al. 2007, Chase et al. 2009, McSporran 2009, Bray et al. 2014a).

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