2. Literature Summary

2.1. Definition

Soft-tissue sarcomas (STS) are a group of non-bone tumors; either visceral or non-visceral in origin and exhibit similar biological behavior such as local invasiveness, post-surgical recurrence after conservative surgery and a low to mild metastatic potential (MAULDIN, 1997; WITHROW, 1998b). Tumor types generally included in this group are fibrosarcoma, malignant peripheral nerve sheath tumor, hemangiopericytoma and malignant fibrous histiocytoma (DERNELL et al., 1998; MACEWEN and WITHROW, 1996; MAULDIN, 1997; PAGE and THRALL, 2000; THRALL and GILLETTE, 1995). Some authors include undifferentiated sarcoma, rhabdomyosarcoma, liposarcoma (THRALL and GILLETTE, 1995), lymphangiosarcoma (FINEMAN, 2000), myxosarcoma and synovial cell sarcoma (PAGE and THRALL, 2000; WITHROW, 1998b) in the soft-tissue sarcoma group, while other authors express uncertainty about the inclusion of rhabdomyosarcoma, lymphangiosarcoma, leiomyosarcoma, and liposarcoma due to their rarity, lack of clinical characterization (WITHROW, 1998b) and insufficient evidence documenting tumor grading (PAGE and THRALL, 2000). Agreement generally exists on the exclusion of lymphoid, hemopoetic and mast cell tumors from the soft-tissue sarcoma group along with osteosarcoma, hemangiosarcoma, chondrosarcoma and malignant melanoma (MACEWEN and WITHROW, 1996; MAULDIN, 1997; PAGE and THRALL, 2000; WITHROW, 1998b).

Although many authors do not restrict the definition of soft-tissue sarcoma by anatomic location (MAULDIN, 1997; PAGE and THRALL, 2000; THRALL and GILLETTE, 1995), oral sarcoma has served as an exclusion criteria in some studies (KUNTZ et al., 1997; MCKNIGHT et al., 2000) and has received attention as a separate clinical entity (BREWER and TURREL, 1982; THRALL, 1981).

2.2. Origins

All causes of soft-tissue sarcomas have not been identified in dogs, although comparative studies have identified several etiologies in other species. The

parasite *Spirocera Lupi* is the only infectious agent that has been shown to have a causal association with fibrosarcoma (FSA) in the dog (BWANGAMOI, 1967; PARTHASARATHY and CHANDRASEKHARAN, 1966), most commonly of the esophagus, but in other sites as well (STEPHENS et al., 1983). Viral etiologies have been associated with connective tissue tumors in other domestic species such as cats (MCKISSICK and LAMONT, 1970), horses (ANGELOS et al., 1991; OTTEN et al., 1993) and chickens, (ROUS, 1983) but have not been linked to naturally occurring connective tissue tumors in the dog and regress spontaneously when experimentally induced (SLAUSON et al., 1975a; SLAUSON et al., 1975b).

Physical and chemical insults have been associated with connective tissue tumors in many species; the pathogenesis of which may involve the inflammation pathway. Under experimental conditions, the implantation of foreign bodies results in connective tissue sarcoma in mice (BRAND et al., 1976); one report exists of foreign-body-associated liposarcoma in the dog (MCCARTHY et al., 1996). Sarcoma formation has been documented at fracture and orthopedic implant sites in humans (KEEL et al., 2001; MCDONALD et al., 2002), and dogs (HARDY, 1976; ROMANELLI, 2001; SINIBALDI et al., 1976) and with ocular trauma in cats (DUBIELZIG, 1984; DUBIELZIG et al., 1990). Evidence from feline medicine has proved an association between vaccine site and fibrosarcoma formation that has recently received attention (HENDRICK et al., 1992); however the exact causative etiology has not been detected although an association with inflammation is suspected.

Heritable soft-tissue sarcomas have been described in some species. Genetic abnormalities in the tumor repressor protein p53 and the retinoblastoma gene have been associated with STS (CANCE et al., 1990; KARPEH et al., 1995; RIESKE et al., 1999). Fibrosarcoma has also been related to the genetic disease von Recklinghausen's in man that is characterized by multiple benign fibrous growths. In some cases, these benign growths progress to malignancy (RICCARDI et al., 1984; RICCARDI and ELDER, 1986; RICCARDI and POWELL, 1989). In dogs, abnormalities of p53 in fibrosarcomas have been described (GAMBLIN et al., 1997) and MDM2 gene amplification has been found in malignant peripheral nerve sheath tumors (MPNST) and rhabdomyosarcoma (NASIR et al., 2001). A disease similar to von Recklinghausen's disease has not been described in dogs.

Soft-tissue sarcomas have also been described to arise as sequelae to treatment. Radiation has been shown to induce wide varieties of cancers including soft-tissue sarcomas that have been reported in the treatment fields of dogs and

humans that received radiation therapy (BLOECHLE et al., 1995; COATESWORTH et al., 1996; MARTIN-HIRSCH et al., 1991; RENNIE et al., 1983; THRALL, 1984). Lymphatic obstruction, most commonly as a sequelae of surgical trauma incurred during mastectomy, has resulted in lymphangiosarcoma in edematous limbs (AUTIO and KARINIEMI, 1999; FEIGENBERG et al., 2002; NEMOTO et al., 1969); a similar association between lymphatic obstruction and lymphangiosarcoma has been suggested in dogs (BARNES et al., 1997).

2.3. Signalment

Soft-tissue sarcomas are most commonly seen in dogs of mixed breeding, (BOSTOCK and DYE, 1980; BREHM et al., 1995; GRAVES et al., 1988; KUNTZ et al., 1997; POSTORINO et al., 1988). Of purebred dogs, German Shepherds, Poodles, Labradors and Boxers are commonly represented in the STS population (BOSTOCK and DYE, 1980; MCCHESNEY et al., 1989b; MILLS and NIELSEN, 1967; POSTORINO et al., 1988). Boxers are unique in that they commonly have hemangiopericytoma (HPC) but rarely fibrosarcoma (BOSTOCK and DYE, 1980). Labradors have been observed to be the most commonly seen patients with FSA (BOSTOCK and DYE, 1980). Two recent reports involving the treatment of STS included a high number of Golden Retrievers (FORREST et al., 2000; MCKNIGHT et al., 2000); as did a study of MFH (KERLIN and HENDRICK, 1996).

Studies conflict on reporting of the distribution of STS according to sex. Discrepancies in the description of sex distribution are found within individual tumor types, as well as between tumor types. Two large studies encompassing multiple types of soft-tissue sarcomas have shown roughly equal distribution between the sexes (KUNTZ et al., 1997; MCKNIGHT et al., 2000) and one study contained a higher proportion of male dogs (FORREST et al., 2000). Three reports of canine hemangiopericytoma have included more female dogs than male dogs with females accounting for roughly 60-70% of all cases (EVANS, 1987; GRAVES et al., 1988; MILLS and NIELSEN, 1967). Two other studies have shown males to be more commonly afflicted with HPC (POSTORINO et al., 1988; YOST and JONES, 1958). Two studies concerning oral FSA did not share consensus on sex distribution; THRALL (1981) reported a greater incidence in male dogs while BREWER (1982) reported a higher incidence in female dogs.

Studies show that soft-tissue sarcoma occurs in older dogs, with a median age of approximately 10 years (BOSTOCK and DYE, 1980; EVANS, 1987; KUNTZ et al., 1997; MCCHESNEY et al., 1989b; MILLS and NIELSEN, 1967). Two recent papers encompassing STS and radiation therapy showed the mean age to be slightly younger, around 8.5 years (FORREST et al., 2000; MCKNIGHT et al., 2000). One study of HPC has shown females to be younger (8.6 years) than males (10 years) at the time of presentation (YOST and JONES, 1958). Median age of liposarcoma and MPNST appearance is similar to other tumor types, 9.7 and 9.2 years respectively (BREHM et al., 1995; STRAFUSS and BOZARTH, 1973). Studies that engage both FSA and HPC show that FSA occurs at a lower age (BOSTOCK and DYE, 1980). Mean age of oral FSA has been reported to be 6.3 (BREWER and TURREL, 1982), 6.6 (SCHWARZ et al., 1991b), and 8.6 (THRALL, 1981) years. Although mean and median ages for most STS tend to be reported in the 8-11 year range, lymphangiosarcoma (BARNES et al., 1997; SAGARTZ et al., 1996) MPNST (ANDERSON et al., 1999), undifferentiated sarcoma (SANDERS et al., 1996) and MFH (PIRES, 1997) have been reported in dogs one-year-old or younger. Aggressive lymphangiosarcoma has been described in a dog as young as eight-weeks of age (SAGARTZ et al., 1996). Similar to human medicine (RANEY et al., 2001), rhabdomyosarcoma is seen in the juvenile population (KIM et al., 1996; SEIBOLD, 1974a; YANOFF et al., 1996).

2.4. Location

All parts of the body can give rise to STS; the anatomical distribution of STS varies with tumor histotype (BOSTOCK and DYE, 1980; FORREST et al., 2000). Several articles describe STS occurring on the limbs and trunk with roughly equal frequency (BOSTOCK and DYE, 1980; FORREST et al., 2000) while other studies show a higher incidence of extremity involvement (KUNTZ et al., 1997; MCCHESNEY et al., 1989b; MCKNIGHT et al., 2000). Tumors of the limbs are reported to be more frequent in the proximal extremity than the distal extremity (KUNTZ et al., 1997).

Some tumor types preferential appear on the limbs such as HPC, which originate in the extremities in 70-75% of all cases (BOSTOCK and DYE, 1980; CONNERY and BELLENGER, 2001; MILLS and NIELSEN, 1967). MPNST and MFH are also more common on the limbs than on the trunk, the front limbs are more commonly affected with MPNST and the rear limbs are more commonly affected with

MFH (BREHM et al., 1995; KUNTZ et al., 1997; WATERS et al., 1994). The trunk follows the limbs as the second most common site for STS (KUNTZ et al., 1997; MCCHESNEY et al., 1989b; MCKNIGHT et al., 2000) and may be a predilection site for liposarcoma (STRAFUSS and BOZARTH, 1973) and anaplastic sarcoma (FORREST et al., 2000).

Fibrosarcoma is the third most common neoplasia of the oral cavity and the most common oral tumor of the STS family (TODOROFF and BRODEY, 1979). Some studies show FSA in the maxillary region more often than the mandibular region (BREWER and TURREL, 1982; CIEKOT et al., 1994) although a greater incidence in the mandibular region has also been reported (THRALL, 1981). Hemangiopericytoma of the head and oral cavity are rare and involvement of the orbit is uncommon (BELTRAN et al., 2001). Malignant peripheral nerve sheath tumors of the oral cavity are rare, but not unknown (HOERSTING et al., 1998). Isolated cases of rhabdomyosarcoma in the oral cavity (LASCELLES et al., 1998; SEIBOLD, 1974b) and laryngopharyngeal regions have been reported (BLOCK et al., 1995; CLERCX et al., 1998; HENDERSON et al., 1991; LADDS and WEBSTER, 1971; MADEWELL et al., 1988). Soft-tissue sarcomas of visceral origin are not unknown, with the spleen receiving the most attention (ROGERS et al., 1994; SPANGLER et al., 1994; WEINSTEIN et al., 1989). Involvement of other structures such as the lower urogenital tract (CLARK. et al., 1984; KELLY, 1973; KIM et al., 1996; KUWAMURA et al., 1998; PEAVY et al., 1992; SENIOR et al., 1993; STAMPS and HARRIS, 1968), diaphragm (ANDERSON et al., 1999), heart (BRIGGS et al., 1997; GONIN-JMAA et al., 1996; KROTJE et al., 1990; PEREZ et al., 1998; VICINI et al., 1986), caudal caval vein (ROBINSON et al., 1998) and kidney (GORSE, 1988; RUDD et al., 1991; VILAFRANCA et al., 1995) have been described.

2.5. Clinical Appearance and Diagnosis

Clinical presentation is dependent on the state of tumor advancement. Initially, signs may be limited to a slowly progressive mass (GRAVES et al., 1988), but functional deficits such as lameness (BREHM et al., 1995) or dysphagia (SCHWARZ et al., 1991b) may be the presenting complaint. Palpation often reveals a semi-firm to firm mass that is non-painful in early stages (GRAVES et al., 1988; MAULDIN, 1997), frequently lobate and hairless (MILLS and NIELSEN, 1967; WATERS et al., 1994; YOST and JONES, 1958). Anchorage to underlying structures

may be detected in roughly half of all cases (POSTORINO et al., 1988). However, free mobility of the epidermis is common (MILLS and NIELSEN, 1967) and may falsely render the impression of a benign condition (WITHROW, 1998b). Enlargement of the regional lymph nodes is often detected, although this is most often not a result of regional metastasis (POSTORINO et al., 1988). Invasion of muscles covered with a heavy fascia may be more commonly associated with pain than invasion of muscles with light fascial covering (MCCHESNEY et al., 1980). Local edema has been described in connection with lymphangiosarcoma (FOSSUM et al., 1998; KELLY et al., 1981).

Local radiographic examination often reveals a mass with increased soft-tissue density of the affected area (GRAVES et al., 1988) and may be useful in detecting bony involvement (BREHM et al., 1995; CIEKOT et al., 1994; POSTORINO et al., 1988). In contrast to the radiographic appearance of other STS, liposarcoma and infiltrative lipoma may appear less dense than surrounding soft-tissue (SAIK et al., 1987; STRAFUSS and BOZARTH, 1973).

Neither blood counts nor serum chemical analysis routinely reflect the presence of STS unless visceral involvement compromises organ function (WATERS et al., 1994). One paper reported increased serum chloride and creatanine phosphokinase (MCCHESNEY et al., 1980). Tumor-related erythrocytosis and leukocytosis have been reported but are considered rare (CHINN et al., 1985; COUTO et al., 1989; GORSE, 1988).

Fine needle aspiration and cytology may be helpful in demonstrating malignant cells, however STS tend to poorly exfoliate cells and this can result in non-diagnostic samples or falsely produce the impression of benign disease (CANIATTI et al., 2001; MAULDIN, 1997). Biopsy is unavoidable for the establishment of a definitive diagnosis (MACEWEN and WITHROW, 1996). Invasive lipomas present a diagnostic challenge, as they resemble benign lipoma on cytological examination and core biopsy. Infiltrative lipomas cannot be diagnosed without direct evidence of invasion on either surgical or microscopic examination (BERGMAN et al., 1994). Dissimilar to the appearance of other STS, lymphangiosarcoma may have cystic structures and surrender modified transudate on aspiration (KELLY et al., 1981).

Following the histopathological confirmation of disease, staging of the patient according to the modified WHO staging system is recommended (POWERS et al., 1995). Thoracic radiography and aspiration of abnormal regional lymph-nodes may prove helpful in detecting metastasis and exploring the extent of disease. Pulmonary metastasis may be visualized on radiographic examination of the thorax,

in some instances accompanied by pleural effusion (SELCER et al., 1984; WATERS et al., 1994). Cross-sectional imaging studies such as CT or MR are useful in some patients to non-invasively investigate the extent of disease and plan subsequent surgical or radiotherapy treatments (MCENTEE and THRALL, 2001; PRESCOTT et al., 1994; SOSTMAN et al., 1994).

2.6. Biological Behavior

STS infiltrate locally and become life threatening if local progression is uncontrollable, encroachment upon vital structures occurs, the tumor presents a severe metabolic burden, significant functional deficits occur, ulceration and infection develop, or deterioration of quality of life requires euthanasia (BREHM et al., 1995; WATERS et al., 1994).

Variation has been reported among tumor type with regard to metastasis, however metastatic rate may be more related to mitotic index or grade than histotype (BOSTOCK and DYE, 1980; KUNTZ et al., 1997). Reported metastatic rates vary among studies, but most values fall in the 8-17 % range (BOSTOCK and DYE, 1980; FORREST et al., 2000; KUNTZ et al., 1997; MCKNIGHT et al., 2000). Two studies showed higher rates of 23.5% (THRALL, 1981) and 70 % (WATERS et al., 1994) but these studies were restricted to oral tumors and giant cell malignant fibrous histiocytoma (MFH) respectively. The lungs are the most common site of metastasis with the regional lymph nodes being the second most common site (KUNTZ et al., 1997). Metastatic disease has been found in the abdominal cavity; this is especially true for liposarcoma (SAIK et al., 1987; STRAFUSS and BOZARTH, 1973).

Dogs with STS of the oral cavity may display more severe clinical signs than dogs with STS of the limbs or trunk as a result of the proximity to vital structures and difficulties incurred in prehension of food or swallowing, either due to pain or steric hindrance (SCHWARZ et al., 1991a; SCHWARZ et al., 1991b). Oral sarcoma has also been reported to metastasize more frequently than STS of other locations (THRALL, 1981).

Fibrosarcoma of the oral structures may behave exceptionally aggressive, despite a benign or non-aggressive histological appearance. These tumors, known as histologically low-grade, yet biologically high-grade fibrosarcomas, are most common in the maxillary region, affect large breed dogs, often invade bone, and have a higher metastatic rate than low-grade sarcomas. When metastasis does occur, the

metastatic lesions often histologically appear as high-grade FSA. Misdiagnosis is common and often reported as nodular fasciitis, fibroma granulation tissue or chronic inflammation; skepticism is recommended if such a histopathological report is returned. Histological low-grade biological high-grade sarcomas are considered to be less responsive to treatment than other fibrosarcomas of the mouth (CIEKOT et al., 1994).

2.7. Pathology

Soft-tissue sarcomas are named for the tissue of origin from which they arise (Table 1). It has been suggested that all spindle cell sarcomas have common precursor cells and histotype represents differences in differentiation pathways more than differences in the tissue of origin. Distinguishing between tumor types may present a diagnostic challenge as many of the tumor types have similar morphological features.

Spindle cells are a consistent feature of STS, but are also found in other sarcomas such as melanoma (RAMOS-VARA et al., 2000). A diagnosis made on light microscopy is based on several factors including nuclear characteristics, tissue architecture, cytoplasmic characteristics, cellular inclusions, staining properties, intercellular material and tissues or structures involved (BOOTH et al., 1998; MAZZEI et al., 2002; POWERS et al., 1995; WATERS et al., 1994; YOST and JONES, 1958). In some cases ultrastructural studies may be helpful, but are not routinely used for diagnostic purposes (DIBARTOLA et al., 1978; MADEWELL et al., 1992; MESSICK and RADIN, 1989; MEYVISCH et al., 1977; SAGARTZ et al., 1996; XU, 1986). Inflammatory infiltration is common in many tumor types and may obscure the diagnosis. Evidence of tumor infiltration into surrounding tissue is useful in confirming the presence of malignancy in some locally invasive tumors such as fibrosarcoma of the face and infiltrative lipoma, which may lack other architectural and cellular hallmarks of malignancy (BERGMAN et al., 1994; CIEKOT et al., 1994).

In cases where microscopic morphology is inadequate in rendering a diagnosis, immunohistochemical stains that reveal the presence of molecular features such as factor VIII, actin, desmin and S100a have utility in identifying tumor histotype and excluding more insidious diseases such as amelanocyitc melanoma and hemagiosarcoma (ANDREASEN and MAHAFFEY, 1987; MADEWELL et al., 1988; MAZZEI et al., 2002; MOORE et al., 1989; MOORE, 1986; PEREZ et al., 1996;

RABANAL et al., 1989; WILLIAMSON and MIDDLETON, 1998). Immunohistochemisty is not limited to biopsy specimens; studies have been conducted on cytological smears (ANDREASEN et al., 1988).

Gross pathological examination often reveals a white to cream colored lobulated mass that palpates fleshy to firm in consistency (GRAVES et al., 1988). Infiltration into surrounding tissues is often noted (BERGMAN et al., 1994; CIEKOT et al., 1994; POSTORINO et al., 1988). A freshly cut slice often reveals hemorrhagic streaking, sometimes accompanied by areas of necrosis. Often the tumor has an encapsulated appearance that consists of compressed tumor cells (MILLS and NIELSEN, 1967).

Type	Tissue of Origin	Microscopic Morphology	Other	Source
Hemangiopericytoma	Pericytes of Zimmerman	"Whorling" around a central vessel; "fingerprint pattern"	Whorling may be absent in recurrent tumors	GOLDSCHMIDT and SHOFER, 1992a; MAZZEI et al., 2002; MILLS and NIELSEN, 1967; YOST and JONES, 1958
Fibrosarcoma	Fibroblasts	"Herring bone" appearance, interwoven pattern	Biologically aggressive oral tumors may appear benign on histopathology	GOLDSCHMIDT and SHOFER, 1992b; MACEWEN and WITHROW, 1996
Malignant Fibrous Histiocytoma	Fibroblasts	Histiocytes present, storiform pattern	Some variants contain giant cells	BOOTH et al., 1998; GLEISER et al., 1979b; KERLIN and HENDRICK, 1996; PEREZ-MARTINEZ et al., 2000; WATERS et al., 1994
Malignant Peripheral Nerve Sheath Tumors	Glial cells	Association with nerve, ovoid nuclei	Nomenclature: Schwanoma, neurofibrosarcoma	GOLDSCHMIDT and SHOFER, 1992c; MACEWEN and WITHROW, 1996
Liposarcoma and Infiltrative lipoma	Adipose Tissue	Lipid inclusion bodies Infiltration of muscle. Otherwise like lipoma	Nomenclature may represent degree of differentiation or two separate tumor types	BERGMAN et al., 1994; BOZARTH and STRAFUSS, 1973; DOSTER et al., 1986; GLEISER et al., 1979a; SAIK et al., 1987; ZWICKER, 1970

Table 1 Pathological characteristics and tissue of origin of selected histotypes included in the STS group.

2.7.1. Tumor Grade

Several grading schemes based on microscopic criteria of malignancy have been examined as indicators of biological behavior of STS (BOSTOCK and DYE, 1980; DERNELL et al., 1998; KUNTZ et al., 1997; POSTORINO et al., 1988). Tumor grade has been shown to play an important role in the prognosis of soft-tissue sarcomas in humans (COINDRE et al., 1988). A grading scheme from human medicine (COINDRE et al., 1988) where necrosis, differentiation and mitotic rate (Table 2, Table 3) are individually scored and summed has been adapted for use in dogs (POWERS et al., 1995) and examined in recent studies (KUNTZ et al., 1997; MCKNIGHT et al., 2000).

Histological grade and mitotic index have been shown to correlate with metastatic rate in dogs treated with surgery (BOSTOCK and DYE, 1980; KUNTZ et al., 1997), but this has not been demonstrated in all clinical studies of STS. A study of the surgical treatment of STS showed mitotic index to be higher in FSA than in HPC and associated with a higher rate of tumor recurrence (BOSTOCK and DYE, 1980). A correlation between grade and survival was not found in a study of dogs treated with a combination of surgery and radiation (MCKNIGHT et al., 2000), nor in a study of the surgical treatment of STS (GRAVES et al., 1988); although MCKNIGHT et al. (2000) contained no high-grade sarcomas, and GRAVES et al. (1988) reported no confirmed case of metastasis.

	Score		
Criteria	**1**	**2**	**3**
Differentiation	Closely resembling adult tissue	Tumors of certain histological type	Tumors of uncertain histological type
Mitosis per 10 x400 field	1-9	10-19	20+
Necrosis	No necrosis	Less than 50% necrosis	Greater than 50% necrosis

Table 2 The criteria necrosis, mitosis count and differentiation are given a score ranging from 1-3.

Total Score	Grade
3-4	I (Low)
5-6	II (Intermediate)
7+	III (High)

Table 3 The three criteria evaluated are summed. Grade is assigned based on sum of the score.

2.8. Therapeutic Modalities

Although surgical resection is the most widely available and employed method of treating STS, other treatment modalities have been reported. Irradiation, chemotherapy and hyperthermia have all been investigated as treatments for sarcoma of the soft-tissue. Many studies exist that report the combination of treatment modalities.

2.8.1. Surgery

Surgery is the most disseminated treatment for visible disease. Surgery undertaken with curative intent often requires amputation or radical resection if adjuvant therapy is to be avoided (BREHM et al., 1995; GRAVES et al., 1988; KUNTZ et al., 1997; POSTORINO et al., 1988).

For the surgical removal of STS, it is recommended that surgical planes of dissection contain only normal tissue 2-3 cm surrounding the tumor (WITHROW, 1998c). As pseudo-encapsulation is a common feature of STS, “shelling-out” such a structure should not be confused with complete removal (WITHROW, 1998c). Any structure attached to the tumor should be excised en-bloc along with the tumor (WITHROW, 1998c). Additional recommendations include conducting early venous ligation to avoid dispersion of malignant cells (WITHROW, 1998b), excision of all previous biopsy tracts and marking all suspicious areas of excised tissue for histopathological evaluations of margins (WITHROW, 1998a). Copious lavage conducted prior to surgical closure may aid in flushing loose tumor cells. Some radiation oncologists advocate marking the boundaries of the surgical field with metal, such as hemoclips or wire to aid in planning radiation therapy in the event of incomplete resection (MAULDIN, 1997).

In dogs, surgery as a lone treatment modality has been reported to achieve local control rates ranging from 60-85% (BOSTOCK and DYE, 1980; GRAVES et al., 1988; KUNTZ et al., 1997; POSTORINO et al., 1988). Local recurrence has been associated with failure to obtain adequate surgical margins, resulting in a recurrence rate 10.5 x higher in dogs where margins are incomplete (KUNTZ et al., 1997; STOJADINOVIC et al., 2002a). When surgical failure occurs, recurrence times are

usually under one year (BREHM et al., 1995; GRAVES et al., 1988; KUNTZ et al., 1997). Amputation has been shown to result in a lower rate of recurrence than limb sparing procedures in humans (COLLIN et al., 1988; STOJADINOVIC et al., 2001b), and is sometimes required due to the difficulty in achieving adequate surgical margins of the distal limb (LAWRENCE, 1994).

Several prognostic factors for recurrence and survival have been identified in humans and dogs. In humans, tumor grade has been shown to influence recurrence and survival, with higher grade tumors being more likely to return or result in death (COLLIN et al., 1988; STOJADINOVIC et al., 2002b). Similar to human sarcomas, mitotic index and grade have been shown to influence recurrence and survival in canines following surgery (BOSTOCK and DYE, 1980; KUNTZ et al., 1997). In contrast to most reports concerning grade, tumor necrosis, which is commonly found in high-grade tumors, was associated with superior survival in one study (POSTORINO et al., 1988). One study of dogs that encompassed several histotypes found that survival was shorter with FSA than HPC, although this was most likely due to the difference in mitotic index of the tumor types (BOSTOCK and DYE, 1980). In humans, tumor type has been associated with surgical failure with rhabdomyosarcoma, angiosarcoma and malignant peripheral nerve sheath tumors being negative prognostic factors (COLLIN et al., 1988). The interval between detection and surgery has been shown to be of prognostic significance in dogs; longer intervals have correlated with a decreased survival rate in canines (POSTORINO et al., 1988). Other negative prognostic factors such as large tumors size and advanced age have been shown to accompany higher rates of recurrence and metastasis in humans (COLLIN et al., 1988; HEISE et al., 1986; SIM et al., 1988; STOJADINOVIC et al., 2001a; TOROSIAN et al., 1988) , but have not been examined in dogs. A summary of studies encompassing surgical treatment of STS in dogs is presented in Table 4.

Authors	N= Design	Inclusion/ Restriction Criteria	Signalment/ Presentation	Survival/Local Control	Prognostic Factors
Graves et al., 1988	Sx only (16); Sx+RT (5)	Restricted to HPC	Tumors were more common in extremities, 70 % female dogs	31% recurrence rate with Sx; 60% recurrence rate with RT + Sx; 38% overall recurrence; no metastasis reported.	No association with mitotic index was found
Bostock and Dye, 1980	235 dogs, 187 were followed	All STS included	HPC common and FSA uncommon in Boxers, HPC in older dogs	Metastasis was more common with FSA (7/74) than HPC (1/86). 80 wk Survival for FSA, 118 wk for HPC; 3-year recurrence rate of 40%.	Size was not prognostic, head had shorter survival interval; FSA had shorter survival times than did HPC; mitotic index was more prognostic than histotype
Postorino et al.; 1988	34 Sx; 8 Sx+RT	Restricted to HPC	Limbs most common site	21% local recurrence; mean time to recurrence was 16 months. No cases of metastasis	Interval from detection to treatment was prognostic for recurrence; tumor necrosis was associated with better prognosis
Kuntz et al., 1997	75 Sx	Multiple histotypes included; Other therapy excluded.	MPNST had fewer mitotic figures	Recurrence in 15% of patients; average time to time to recurrence 368 days; average time to metastasis 365 days. 17 % metastasis	High metastatic rate (41%) for Grad III sarcoma; grade is prognostic for survival; dirty margins have a 10x greater chance of recurrence
Brehm et al., 1995	51 (Sx) 9 peripheral, 20 plexus, and 23 root tumors.	Restricted to MPNST		Prognosis, 1/9 peripheral recurred (no survival data), 12 month for plexus and 5 months for root	Peripheral tumors had a better prognosis than plexus or root tumors

Table 4 Summary of selected publications of survival and local control for the surgical treatment of STS and prognostic factors identified in dogs.

(FSA=Fibrosarcoma, HPC=Hemangiopericytoma, MPNST= Malignant peripheal nerve sheath tumor, Sx=surgery, RT=Radiation treatment, wk=week)

2.8.2. Chemotherapy

Compared to normal tissue, solid tumors have dilated, torturous vessels with disorganized and incomplete basement membranes (RICHARDSON, 1985). Although blood flow through a tumor may be increased compared to surrounding healthy tissue, overall tumor perfusion may be reduced and heterogeneous. Irregular hemodynamics in combination with increased interstitial pressures in tumor tissue influence the pharmacokinetics and distribution of large molecular drugs (DEWHIRST et al., 1995; GRIFFON-ETIENNE et al., 1999). Altered fluid dynamics in solid tumors may be important in explaining the lack of activity of cytostatic agents (RICHARDSON, 1985). Additionally, many cell-mediated mechanisms of chemotherapy resistance have been identified which may contribute to failure of chemotherapy (BERGMAN and OGILIVE, 1995).

Chemotherapy has been examined in human medicine as a single agent, adjuvant and neo-adjuvant therapy. Intraarterial chemotherapy has been reported to be of benefit prior to performing cytoreductive surgery (HENSHAW et al., 2001), although this practice does not enjoy universal approval (BRENNAN, 2001). The utility of chemotherapy in humans with high-grade sarcoma or undergoing limb-sparing procedures has been shown in several studies although the benefit may be limited (BENJAMIN, 1999; BRENNAN, 2001; EDMONSON, 1994; FERNBERG et al., 1999; FRUSTACI et al., 2001; LEJEUNE et al., 2000; PICCI, 2000). Consensus has not been achieved concerning the optimal protocols or indications for using chemotherapy in human STS patients.

Few reports exist concerning chemotherapy as a sole treatment modality for soft-tissue sarcomas in dogs. Expert opinion is that chemotherapy is not an effective treatment modality when used alone in the presence of macroscopic disease and may result in added toxicity without added benefit (LARUE and VUJASKOVIC, 1995; MAULDIN, 1997). However, chemotherapy with doxorubicin, cis- or carboplatin may be of benefit with high-grade STS but evidence supporting this recommendation is lacking (PAGE and THRALL, 2000).

Several phase II studies exist that examine the effectiveness of cytostatic agents against a wide variety of tumors. Soft-tissue sarcomas were among the tumors studied during the phase II examinations of mitoxantrone, doxorubicin, methoximorpholino-doxorubicin and ifosfamide (HERSHEY et al., 1999; OGILVIE et

al., 1989; OGILVIE et al., 1991; RASSNICK et al., 2000; SHEAFOR et al., 2000). Most phase II studies have included only a limited number of animals with STS, with the exception of the doxorubicin study that contained 26 animals and resulted in partial or complete remission in four dogs. Stabilization was reported in a large number of animals, however the criterion for stabilization was an increase in tumor size not exceeding 50% increase over a six-week period, which may be consistent with slowly progressive disease. None of the above mentioned drugs examined showed consistent efficacy in treating macroscopic disease. Various formulations of intralesional cisplatin have been examined and may be useful in the treatment of macroscopic disease although local tissue reaction has been problematic (DERNELL et al., 1997; THEON et al., 1991; TOZON et al., 2001).

2.8.3. Radiation

Radiation can be administered with the goal of long-term local control and tumor regression or with the goal of palliation and an improvement in quality of life without the expectation of a long-term increase in survival.

2.8.3.1. Physics and Biology

The premise of radiation therapy is that radiation can be deposited on a tumor in a fashion that damages DNA in tumor cells while normal tissues are spared by their inherent ability to repair damaged DNA (THRALL, 1997). Radiation delivery in veterinary medicine is usually by means of an external beam (LARUE and GILLETTE, 1996), although the use of implanted radiation sources (brachytherapy) has been reported in veterinary medicine (TURREL and KOBLIK, 1983).

External beam irradiation is often classified by beam energy. Energy exceeding 1 million electron volts is termed megavoltage radiation (MV) and energy under 1 million electron volts is referred to as orthovoltage radiation (GILLETTE and GILLETTE, 1995). Several characteristics of external beam radiation such as penetration depth and tissue absorption depend on emitted radiation energy. Orthovoltage delivery units emit beams ranging from 150 to 300 kilovolts (KV) in energy (THRALL et al., 1988). The lower energy photons emitted from orthovoltage machines do not penetrate deeply. Energy is deposited on the skin and superficial

structures and preferentially absorbed by more radiodense structures such as bone. A drawback of orthovoltage radiation is that the treatment of deeper structures is often limited by superficial toxicity (THRALL et al., 1988).

Megavoltage radiation is most commonly obtained either from linear accelerators or from isotope sources, with the trend being towards the installment of linear accelerators (BURK and GIEL, 1997). Linear accelerators produce higher peak photon energies than cobalt units; units that deliver radiation in the 4-25 MV range are widely accessible in human medicine (WALKER, 1997). The higher energy photons allow for deep penetration and afford a skin-sparing effect. Cobalt-60 is a commonly used isotope in radiation therapy that produces megavoltage (1.2-1.5 MV) ionizing radiation as a product of nuclear decay. Cobalt machines offer many of the advantages of high-energy irradiation such as deeper penetration and a skin sparing effect, however the energy produced by cobalt-60 is lower than is available with modern linear accelerators (BURK and GIEL, 1997).

The radiation dose describes the amount of energy deposited per volume of tissue; the gray (Gy) is the standard unit of radiation dose (1 joule / kilogram) (HALL, 2000c).

External beam radiation is given in a series of treatments, known as fractions, to a total prescribed dose. Fractionated delivery offers several radiobiological advantages in sparing healthy tissue such as allowing for repair of sublethal damage and repopulation of depleted cells. At the same time, the elimination of tumor cells results in decreased diffusion distances and increased oxygenation of tumor tissue (BRIZEL et al., 1996; ZEMAN et al., 1993). Cellular oxygen reacts with radicals produced by ionizing radiation to produce organic peroxides that react with DNA and “fix” cellular damage (HALL, 2000d). Tumor re-oxygenation may increase the effectiveness of the next radiation fraction. Between delivery of fractions reassortment may occur, that is, tumor cells that were previously in radiation resistant portions of the cell cycle may enter more radiosensitive phases of the cell cycle (HALL, 2000e).

An increased number of fractions allows for increased radiation tolerance of healthy tissue and a higher total dose, which may be associated with superior tumor control (ANDERSON et al., 2002). In human medicine, fine fractionation schedules are common, in some cases twice-daily fractions are delivered with total doses that exceed 80 Gy (HALL, 2000e). In veterinary medicine, such fine fractionation schedules are rare due to the added risk and expense incurred by the necessity of anesthesia for each treatment (THRALL, 1997).

2.8.3.2. Toxicity

Radiation damage to DNA, in both healthy and tumor cells, results in cell death, loss of reproductive capacity and altered cellular function. The amount of radiation that can be safely delivered to cancerous tissue is limited by collateral damage inflicted upon surrounding healthy tissue. Radiations protocols should be designed such that severe complications do not occur in more than 5% of patients treated (GILLETTE et al., 1995).

Radiation toxicities can generally be divided into two groups: acute and late toxicities. Rapidly proliferating tissues such as tumor cells, epithelial or hemolymphatic cells show the effects of radiation quickly and often suffer acute toxicity. More slowly dividing tissue such as connective tissue, nervous tissue or bone show toxic effects later (HARRIS et al., 1997). Possible long-term consequences to all healthy tissue included in the radiation field should be assessed prior to beginning radiation treatment (LARUE et al., 1995). Factors that influence the degree of toxicity include total dose, dose rate, dose per fraction and field size (HARRIS et al., 1997; LARUE and GILLETTE, 1996). Some pharmacological substances such as doxorubicin, cisplatin, and metronidazole may act as radio-sensitizing agents and increase radiation reactions in healthy tissues (HARRIS et al., 1997).

2.8.3.2.1. Early Reactions

Acute reactions are most often found in rapidly dividing tissues such as the skin, oral mucosa, gastrointestinal tract, hematopoetic and lymphatic organs, and vagina. Skin reactions are readily visible and may be painful and uncomfortable, but usually resolve with minimal treatment and are seldom dose limiting when high energy radiation is used. Initial radiation insult may result in dermal erythema due to capillary dilatation of the superficial dermis. Additional exposure may progress through the stages of dry desquamation, moist desquamation and ulceration. Dry desquamation is due to the decreased proliferation of epithelium and presents as thinning of the skin and dry scales. During this second stage, swelling of the endothelium results in capillary obstruction. Adenxeal structures may also cease to function and epilation may occur (HALL, 2000a; HARRIS et al., 1997). Mitotic death of epidermal germ cells may result in moist desquamation, accompanied by

epidermal sloughing, shedding of the supra-epidermal bulla, fibrinous exudate and persistent edema. Moist desquamation is usually at its worst 1-2 weeks after the completion of treatment (HARRIS et al., 1997). Discomfort caused by radiation injury may result in self-mutilation if preventive measures are not undertaken, such as the use of an Elizabethan collar (HARRIS et al., 1997). Injury can be worsened if bandages, casts or petroleum based ointments are included in the radiation field as these substances may act as a bolus and increase energy deposited on the skin during subsequent radiation treatment and inhibit resolution of radiation injury (GILLETTE et al., 1995). Both dry and moist desquamation will usually uneventfully resolve 2-4 weeks after their appearance (GILLETTE et al., 1995). In more severe cases, dermal injury may be managed with corticosteroids and infection controlled with topical or systemic antibiotics (MCKNIGHT et al., 2000).

2.8.3.2.2. Late Reactions

Late effects are most commonly seen months to years after radiation exposure in non-renewing tissues such as bone, lung, heart, kidneys, eyes, great vessels, trachea, soft-tissue, spinal cord and other slowly or non-proliferative tissues (GILLETTE et al., 1985; LARUE and GILLETTE, 1996; MCCHESNEY et al., 1988; MCCHESNEY et al., 1989a; POWERS et al., 1987) and are usually permanent, irreversible, and carry a poor prognosis (HARRIS et al., 1997). Late effects are usually dose limiting in radiation therapy and the manifestation of late radiation toxicity may require surgical intervention (DERNELL and WHEATON, 1995b; HALL, 2000a). Late reactions result from the elimination of germ cells, sterility of reverting post-mitotic cells and dysfunction of post-mitotic cells. Radiation damages blood vessels and results in sub-optimal perfusion that may aid the progression of late toxicity. In connective tissue, fibrosis and necrosis may result; vascular compromise limits access to cellular components of the immune system and opens the potential for infection. Radionecrosis in bone and soft-tissue are generally non-responsive to conservative therapy (GILLETTE et al., 1995; POWERS et al., 1989), although some reports of success have be reported in humans that received hyperbaric oxygen treatment (ASHAMALLA et al., 1996a; ASHAMALLA et al., 1996b; VIDETIC and VENKATESAN, 1999). Damage to bone is caused by vascular changes and loss of cellularity (LARUE et al., 1987) and may manifest as pathologic fracture or septic radio-osteonecrosis caused by the lack of immune cells accessing the Halversian canals (DERNELL and WHEATON, 1995a; LARUE et al., 1987). Parenchymous

organs suffering from late radiation effects may cease to function and result in life threatening complications.

Secondary tumors in the radiation field have been described in humans and dogs. In humans, secondary tumor formation has been well documented in tumors of the head (BONETTA et al., 1996; HARTLEY, 1993; PATEL et al., 1999; RENNIE et al., 1983; SPRAGGS et al., 1994; ZACHARIADES et al., 1985) and in other anatomic sites (BLOECHLE et al., 1995; CEFALO et al., 1997; EVANS and HUGHES, 1978; MURRAY et al., 1999; VAN CASTEREN et al., 2001). In dogs, squamous cell carcinoma, fibrosarcoma and osteosarcoma have been observed to occur in radiation treatment fields (MCKNIGHT et al., 2000; POWERS et al., 1989; THEON et al., 1997b; THEON et al., 1997a; THRALL et al., 1981).

The late effects of radiation may be minimized by implementing protocols that deliver a larger number of smaller dose fractions. The inherent ability of normal tissue to repair sub-lethal damage to be repaired may allow for higher total dose with fine fractionation while limiting late radiation toxicity at an acceptable level (HALL, 2000a; HALL, 2000e).

2.8.3.3. Irradiation of Measurable Disease

Measurable STS are considered resistant to radiation. Radiation therapy is generally no longer delivered as a lone modality if surgery is possible, although small tumors may be controllable with high doses of radiation in humans (SUIT and SPIRO, 1994). Tumor stabilization is generally between 1-2 years when a definitive protocol is delivered, with higher doses resulting in a superior progression free interval. Hemangiopericytoma has been reported to be more readily controlled than FSA, and regression of tumors of the head occurs more rapidly than do tumors of the extremities (MCCHESNEY et al., 1989b). In contrast to other STS, infiltrative lipoma may be controlled with radiation as a lone treatment modality (MCENTEE et al., 2000). The addition of local chemotherapy such as intra-lesional cisplatin to radiation therapy may aid in local control (THEON et al., 1994). Radioprotectors such as Amoifodtine (WR-2721), a radical scavenging phosphorothioate pro-drug that is selectively activated in healthy tissue and protects against radiation damage, have been examined in human medicine (HALL, 2000c), but have not been shown to be of benefit in dogs (MCCHESNEY et al., 1986).

Hyperthermia is the elevation of local or systemic temperature for therapeutic purposes. Although hyperthermia shows little promise as a lone modality, it has been investigated as an adjunct to radiation therapy in the treatment of canine STS (BREWER and TURREL, 1982; DEWHIRST and SIM, 1984; LARUE and VUJASKOVIC, 1995; PAGE and THRALL, 1990; PAGE and THRALL, 1994). The method of action involves direct cytotoxic effects as well as radiation-sensitizing effects. The lack of normal vascular response to thermal insult (i.e. vasodilatation) may result in enhanced cytotoxicity in tumor tissue compared to normal tissue. Cancerous cells may also be ill-prepared to respond to increased temperature and may be inherently less resistant to increased temperatures than healthy tissue (HALL, 2000b). The effects of hyperthermia are bi-phasic. At lower temperatures hyperthermia acts synergistically with radiation by inhibiting radiation damage repairing pathways, improving oxygenation status (BRIZEL et al., 1996; VUJASKOVIC et al., 2000) and acting on S-phase cells, which are less sensitive to radiation (HALL, 2000b). At higher temperatures tumor vasculature may receive thermal damage resulting in tumor thrombosis and less resistance of nutritionally deprived cells that are found in oxygen deprived and low pH states (VUJASKOVIC et al., 2000).

Several studies have documented the addition of hyperthermia to radiation treatment (GILLETTE, 1982; PROSNITZ et al., 1999; RYU et al., 1996). In dogs, it has been demonstrated that the mean duration of control of STS is increased to approximately 18 months by the addition of hyperthermia, but the chance of obtaining remission is not increased (GILLETTE et al., 1992). The elevation of systemic temperature may be useful in obtaining a more uniform thermal distribution in the tumor, but a benefit in control has not been observed and this practice may be associated with additional complications (THRALL et al., 1996). Studies of radiation and STS that have been conducted in dogs are summarized in Table 5.

2.8.3.4. Irradiation of Residual Disease: Surgery Combined with Radiation

In human medicine, the combination of surgery and radiation has greatly reduced the need for ablative surgical procedures, combined treatment has a reported local control rate of 80-90% (BALDINI et al., 1999; BERTUCIO et al., 2001; HERBERT et al., 1993; PARSONS et al., 2001; PROTT et al., 1999; SUIT and SPIRO, 1995). The premise of combining surgery and radiation is that radiation can

be used to sterilize any cells that are not in the visible surgical field that would otherwise present as clonagens in cases of marginal excision. The cells extending beyond visible disease may have a higher growth fraction, be better oxygenated and more radiosensitive than clonagens residing in gross lesions. Radiation can be delivered before or after cytoreduction, postoperative delivery is more common in veterinary medicine although pre-surgical radiation does offer some advantages and is not without advocates in treating dogs (MAULDIN, 1997).

In humans, studies that engage both pre- and post-operative radiation have shown higher rates of control with preoperative RT (POLLACK et al., 1998). In cases of large tumors, preoperative radiation may allow tumor regression and sterilization of margins so that operative removal is possible. It has been argued that preoperative radiation may decrease vital tumor cells dislodged during surgical manipulation and lower the risk of metastasis, although this has not been proven in dogs (MCLEOD and THRALL, 1989). The tumor blood supply is also undisturbed by a surgical procedure which may avoid areas of hypoxia (MAULDIN, 1997). The radiation field may actually be smaller as the entire surgical field with a healthy margin is irradiated if the tumor is removed prior to surgery (MCLEOD and THRALL, 1989; NIELSEN et al., 1991).

On the other hand, postoperative irradiation allows for the immediate reduction of the tumor burden, immediate palliation and improved cosmesis in cases of large, painful, discharging or disfiguring tumors (LARUE and VUJASKOVIC, 1995). Healing of the surgical wound occurs in tissue that has not been compromised by the effects of irradiation and is associated with fewer complication (MCLEOD and THRALL, 1989). Tumor reduction to microscopic disease alleviates tumor hypoxia, may increase growth rate and render remaining cells more susceptible to radiation or chemotherapy (MAULDIN, 1997; ROSENTHAL, 1996), however surgical disruption of the blood supply may also create areas of low oxygen tension. Histology of the excised tumor is easier to assess if not irradiated prior to pathological review (FORREST, 1997).

Prognostically, tumors of the hind-limb may be more favorable when treated with surgery and radiation and a smaller field size may be advantageous (EVANS, 1987). Oral tumors are associated with inferior survival compared to tumors of the trunk or limbs, but a significant difference in local control has not been demonstrated (FORREST et al., 2000). No studies have documented significant differences in local control according to tumor type or grade. Claims of a benefit achieved by the addition of acemannan to the treatment regime of surgery and radiation are not remotely

supported by properly designed studies (KING et al., 1995). Two recent studies have focused on the use of radiation in combination with surgery.

A study conducted at the University of Wisconsin included 37 dogs that received radiation after incomplete surgical excision of STS (FORREST et al., 2000). Radiation was delivered with a linear accelerator to a total dose ranging from 42-57 Gy. Of the dogs involved in this study 31.4% experienced local recurrence and 14.3% developed metastasis. Tumor control for the first year was 71% and 57% of all tumors were locally controlled at 3 years. Dogs that were treated for oral tumors had significantly shorter survival intervals than did dogs that were treated for tumors of the limbs and trunk, but oral tumors did not show a significant difference in local control when compared to tumors of the trunk and limbs. Dogs with oral sarcoma had a median survival of 540 days, compared to 2,270 days for dogs with tumors of other locations. Although no significant difference in survival or local recurrence was found between histological tumor types, dogs with HPC showed higher rates of control at 3-years (85%). Tumor grade was not shown to be a significant prognostic factor in this study.

A recent study from the Animal Medical Center (New York) followed 48 dogs with incomplete surgical excision of soft-tissue sarcomas that received adjuvant irradiation from a cobalt source (MCKNIGHT et al., 2000). In this study, tumors of the oral cavity were excluded and analysis was based on survival, not local recurrence. One and 2-year survival rates were 87% while the 3 year survival rate was at 81%. Sixteen-percent (n=8) of the dogs in this study developed local recurrence with a median time to recurrence of 700 days. Survival was shown to be negatively impacted by local recurrence and the development of metastasis. Histotype, anatomic location, tumor grade, and field size were not found to be of prognostic significance in this study. Selected studies concerning the use of radiation in the treatment of STS are summarized in Table 5.

Authors	N =; inclusion criteria	Therapy	Survival/Recurrence	Prognostic factors	Other
McKnight et al. (2000)	48, oral STS excluded	MVRT (63 Gy) + Sx	16% recurrence, 1-year survival 87%, 3-year 81%, 5-year 76%	Recurrence and metastasis were prognostic for survival	No high-grade sarcoma were represented
Forrest et al. (2000)	35 (37tumors) resected STS	MVRT (42-57 Gy) + Sx	Median survival 1.5-years with oral sarcoma, 6.2 years with non-oral sarcoma	Oral sarcoma showed inferior survival	10 oral tumors were present, 27 non-oral
McChensey et al. (1989)	42, prospective stratified study	MVRT (35-50 Gy)	50%, 1-year control rate with 45.3 Gy	HPC are more readily controllable than FSA	Higher RT doses offer longer control interval
Evans (1987)	20 (22 tumors)	OVRT (40-50 Gy) + Sx	60%, tumor free at 1-year, 40% tumor free at 2-years	Field size was a prognostic factor	Limited to Hemangiopericytoma
Theon et al. (1994)	12 received RT, 24 total, controlled study	Cis (IT) vs. Cis (IT)+ MVRT, variable dose	Response in all dogs, total tumor clearance in 8 dogs, response ranged from 2-104 weeks in duration	N/A	Recurrence common in peripheral treatment field
McChensey et al. (1986)	73, controlled study	MVRT vs. MVRT + WR2721		Superior control at higher doses	Evaluation of WR-2721, no advantage noted
McChensey et al. (1992)	64, controlled study	MVRT+HT vs. MVRT	Treatment dependent	FSA and high-grade tumor resulted in a quicker regression	Local control was prolonged with HT and RT
Thrall et al. (1996)	64, controlled study	HT+ MVRT vs. WBHT+ MVRT	7-10 months median control	Grade prognostic for local control	No obvious benefit of WBHT found

Table 5 Summary of selected studies concerning soft-tissue sarcoma and radiation (HT=Hyperthermia, OVRT=Orthovoltage Radiation Therapy, MVRT=Megavoltage Radiation Therapy, WBHT=Whole Body Hyperthermia, FSA=fibrosarcoma, HPC=Hemangiopericytoma, Cis=Cisplatin, Gy=Gray, IT=Intratumoral).

2.9. Special Considerations of Oral Sarcoma

Fibrosarcoma is the third most common malignancy of the oral cavity following melanoma and squamous cell carcinoma (TODOROFF and BRODEY, 1979). Recommendations for the local treatment of oral sarcoma are similar to those for the treatment of STS other anatomic locations, namely excision of visible disease and adjuvant radiation in situations when complete excision is unrealistic, possibly with the addition of chemotherapy (BURK, 1996).

Compared to tumors of the trunk and limbs, surgical excision of oral sarcoma is often complicated by bony invasion and proximity of vital anatomic structures. Aggressive surgical procedures such as madibulectomy or maxillectomy are often required to achieve complete excision (KOSOVSKY et al., 1991; SCHWARZ et al., 1991a; SCHWARZ et al., 1991b; WALLACE et al., 1992). Resection of the mandible can result in deficits in cosmesis and function such as tongue lag and mandibular drift that may require additional surgeries to compensate for deficits resulting from surgical excision. Chiloplasty may reduce tongue-lag and reduction or extraction of the canine teeth may alleviate palatine damage caused by malocclusion (KOSOVSKY et al., 1991; SCHWARZ et al., 1991a).

Most studies of oral fibrosarcoma report survival rates of approximately one-year when treated with surgery alone. Studies show mandibular resection resulting in median survival of 10.6–14 months (KOSOVSKY et al., 1991; SCHWARZ et al., 1991a). Of tumors of the maxilla, fibrosarcoma recurred in 57% of all cases treated with aggressive surgery and median survival was 9 months (SCHWARZ et al., 1991b). A meta-analysis of 5 studies showed a median survival time of 12-months, and a local recurrence rate of 37% for the surgical treatment of oral FSA (OGILVIE and MOORE, 1995). A poorer prognosis has been associated with tumors in the caudal oral cavity and with larger tumors (SCHWARZ et al., 1991a; SCHWARZ et al., 1991b; THEON et al., 1997b).

The use of orthovoltage radiation in treating macroscopic disease has been reported to result in a mean progression free interval of four-months and an average survival of 6.4-months (THRALL, 1981). A mean progression free interval of 10.9-months has been reported when hyperthermia was added to orthovoltage radiation. Half of the dogs were in remission at one year and mean overall survival was 13.9-months (BREWER and TURREL, 1982).

The use of megavoltage radiation has shown superior survival compared to orthovoltage studies. Irradiation of 28 FSAs to 48 Gy resulted in a median progression-free interval of 23 months (THEON et al., 1997b). The addition of surgery to radiation in a limited number of cases showed a median survival of 18 months, which was significantly less than STS of non-oral sites (FORREST et al., 2000). Several therapeutic approaches have been undertaken with histologically low-grade biologically high-grade FSA but no treatment has been proven to be superior but surgical excision is recommended, possibly in combination with chemotherapy or radiation (CIEKOT et al., 1994).

Radiation toxicity of the head presents special concerns. The eyes and associated structures are exquisitely sensitive to the effects of radiation; early and late toxicities may be complicated if portal design mandates their inclusion in the radiation field. Ocular irradiation results in early toxicity such as keratoconjunctivitis, blepharitis and atrophy of the corneal epithelia and long term effects such as dry eye, cataracts, retinal degeneration, nasolacrimal scarring and demyelination of the retinal nerve (CHING et al., 1990).

Irradiation of the oral cavity may result in mucositis that is most severe during the last week of therapy (THEON et al., 1997b). Clinical signs include salivation and pain resulting in the refusal to eat or drink (GILLETTE et al., 1995). Oral nasal fistula formation and bone necrosis are long-term complications that may require surgical repair (ADAMS et al., 1987; THEON et al., 1997b; THEON et al., 1997a). Treatment of caudal tumors of the oral cavity have been reported to have higher rates of complications than rostral tumors of the oral cavity (BURK, 1996; THEON et al., 1997b; THEON et al., 1997a). As is the case with non-oral tumors, neoplasia in the radiation field has been reported as a possible consequence of RT and the oral cavity may be a predilection site for radiation induced tumors (MAHMOUD, 1980; PATEL et al., 1999; THRALL et al., 1981). Selected studies concerning the treatment of oral sarcoma are summarized in Table 6.

Authors	N=	Treatment	Survival/Control	Prognostic factors
Kosovsky et al. (1991)	19 FSA (142 total)	Partial mandibulectomy	10.6 months survival	Younger dogs showed superior survival
Schwarz et al. (1991)	14 FSA (61 Total)	Partial maxillary resection	9.5 months median survival	Caudal tumors have a worse prognosis
Schwarz et al. (1991)	13 FSA (81 Total)	Mandibular resection	11 months median survival	Caudal tumors carry a worse prognosis
Theon et al. (1997)	28 (105 total).	MVRT (48 Gy)	29.7 months median local control.	Stage was prognostic
Brewer and Turrel (1982)	10	OVRT (32-48Gy)+ HT (43c)	DFI 434 days, survival 498 days	Not examined
Thrall (1981)	17	OVRT (42.5-45 Gy)	DFI 3.9 months and survival of 6.9 Months	Not examined

Table 6 Summary of selected publications concerning the treatment of oral sarcoma with surgery or radiation. (OVRT= Orthovoltage radiation therapy, MVRT= Megavoltage radiation therapy, HT=Hyperthermia, FSA=Fibrosarcoma, DFI=Disease free inerval, Gy=Gray)

2.10. Special Considerations of Palliation and Reirradiation

Hypofractionated protocols deliver a few large dose fractions with the intent of palliation or exploiting the sensitivity of some tumor types such as melanoma to coarse fractionation (BATEMAN et al., 1994a). The goal of a palliative radiation is to provide pain-relief, improve function and enhance quality of life without the hope of long-term control or eradication of the tumor, although a measurable benefit in tumor control may be noted. The mechanism of palliation is unclear but utility in treating cancer associated pain has been reported in several studies (BATEMAN et al., 1994b; SIEGEL and CRONIN, 1997; THRALL and LARUE, 1995).

Coarse fractionation offers advantages in quality of life improvement, toleration, and cost and time commitment as well as reduced risk for anesthesia. The optimal dose-fractionation schedule is still unknown in dogs (SIEGEL and CRONIN, 1997), but several reports exist in the 3-4-dose range of 8-10 Gy for use in the treatment of thyroid carcinoma, melanoma and osteosarcoma (BLACKWOOD and DOBSON, 1996; BREARLEY, 2000; MCENTEE, 1997; RAMIREZ, et al., 1999). Seventy-four percent of dogs receiving a hypofractionated radiation protocol for the treatment of OSA experienced a decrease in pain or lameness with a median duration of 73 days. Several studies have shown hypofractionated protocols to be well tolerated in dogs (BLACKWOOD and DOBSON, 1996; BREARLEY, 2000; RAMIREZ, et al., 1999). Limited reports exist in veterinary medicine concerning STS and palliative radiation; three undifferentiated sarcomas have been described that received three fractions of 800 cGy on days 0, 7 and 21 as part of a larger study that included a total of 24 dogs with a wide variety of cancers (BATEMAN et al., 1994b). The study was somewhat limited by the difficulty to objectively assess improvement in the quality of life or palliation effects experienced by the patients involved in the study.

In some instances when local control is lost following a course of radiation, re-irradiation may be pursued to control or palliate a recurrent or progressing tumor, however this may be associated with additional toxicity and the risk of late-effect complication may be increased. One study showed a 38% control rate for recurrent/progressive tumors included a variety of tumors in dogs and cats (TURREL and THEON, 1988); severe reactions were seen in only 12% of all animals. Large

irradiation fields and a short interval between the courses of radiation therapy correlated with a higher rate of complications.