The Vet Education Live Web-Seminar (Webinar) Series

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“Soft Tissue Sarcomas”

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SOFT TISSUE SARCOMAS

GENERAL CONSIDERATIONS

Epidemiology
- STS are a diverse group of tumors accounting for 15% and 7% of cutaneous and subcutaneous tumors in dogs and cats, respectively, and 1% of all malignancies
- STS associated with radiation therapy, trauma, foreign bodies (i.e., orthopedic implants), and parasites (Spirocerca lupi)
- radiation therapy increases risk of STS by 2-fold and HSA by 16-fold in women with breast carcinoma

Signalment
- no breed or sex predilection
- rhabdomyosarcoma can occur in animals as young as 4 months

Biologic Behaviour
- STS are considered as a collective due to similar biologic behaviour and histologic features
- sites: cutaneous or subcutaneous tissue and particularly trunk, mammary glands, limbs, and head
- pseudoencapsulated soft to firm tumors with poorly defined histologic margins or infiltrate through and along fascial planes and are locally invasive
- local recurrence after conservative surgery is common
- metastasis through hematogenous routes in up to 50% depending on histologic grade
- regional lymph node metastasis is uncommon (except for histiocytic sarcomas and synovial cell sarcomas)
- histologic grade is predictive of outcome and tumor margins are predictive of recurrence
- poor response to chemotherapy and radiation therapy with gross disease (i.e., > 5 cm diameter)

CLINICAL FEATURES

Clinical Signs
- slowly growing and non-painful mass
- rapid tumor growth can be caused by rapid cellular proliferation, intratumoral hemorrhage, or necrosis
- symptoms related to site of involvement and invasiveness of tumor
- paraneoplastic hypoglycemia with leiomyoma and leiomyosarcoma
- intra-abdominal STS can cause vomiting, diarrhea, and melena with weight loss and anorexia
- nerve root or plexus peripheral nerve sheath tumor can cause pain, lameness, muscle atrophy, and paralysis

Diagnosis
- FNA is recommend to rule out differentials such as lipoma, seroma, inflammation, and abscess
- however, definitive diagnosis of mesenchymal tumors from FNA cytology is difficult because of poor exfoliation, high degree of necrosis which can result in false-negatives, and similar histologic appearance of mesenchymal cells in non-neoplastic, benign, and malignant diseases
- FNA of lymph node often more rewarding as metastatic nodes contain pure population of neoplastic cells compared to the primary tumor which is often heterogenous and contains high degree of matrix
- needle-core, incisional, or excisional biopsy is recommended for definitive preoperative diagnosis and planning
- biopsy is planned so surgical treatment or radiation therapy is not adversely affected
- thoracic radiographs for pulmonary metastasis
- regional imaging (i.e., radiographs, ultrasound, CT, or MRI) if mass is fixed to underlying structures
- ultrasound and CT increase extent of local tumor margins in 19% and 65% of cases, respectively

Histology and Histologic Grade
- histologic features overlap between STS and also other tumor types hence diagnosis can be difficult
- immunohistochemistry with monoclonal and polyclonal antibodies to various tissue markers has improved diagnosis in humans and, to a certain extent, animals
- immunohistochemistry still has considerable overlap in staining patterns between different tumor types
- markers include intermediate filaments (vimentin and desmin), neurofilament proteins, muscle-specific markers (actin, myoglobin and desmin), S-100 (small calcium-binding modulator proteins involved in cell-cycle
progression, cellular differentiation and cytoskeletal membrane interactions and found in glial, Schwann and satellite cells of the nervous system and benign and malignant melanoma, although can also be seen in CSA and ductular epithelial tumors which limits usefulness)

- histologic grade is based on degree of differentiation, mitotic figures, and necrosis

**SURGICAL MANAGEMENT**

**General Considerations**
- surgery is recommended for STS
- STS grow along the path of least resistance and compress and invade surrounding tissue
- STS form a pseudocapsule of compressed and viable tumor cells and marginal resection will be incomplete
- satellite lesions have been detected in surrounding tissue at considerable distance from primary STS in humans
- minimum of 3 cm margins laterally and 1-2 fascial planes deep with dissection
- areas of fixation and biopsy tracts should be excised en bloc with mass
- 2nd surgical resection or radiation therapy for incompletely resected STS
- amputation provided excellent control of local disease but does not affect metastasis or survival time

**CHEMOTHERAPY**

**General Considerations**
- indications: palliative for measurable STS and grade III STS
- efficacy of chemotherapy is unknown in preventing or delaying local recurrence or metastasis
- 15%-27% response rates with most responses short-lived
- intensive neoadjuvant chemotherapy (with intra-arterial cisplatin, doxorubicin, and ifosfamide) for high-grade STS in humans followed by surgery can decrease the need for limb amputation or adjunctive radiation therapy and increase the chance of successful limb-sparing surgery

Doxorubicin
- doxorubicin is the best single agent chemotherapy
- dose: 30 mg/m2 IV every 2-3 weeks for 4-6 treatments
- overall response rate 15%-22%
- response rate better for poorly differentiated rather than well-differentiated STS

Mitoxantrone
- mitoxantrone is a good substitute for doxorubicin in cats
- dose: 5 mg/m2 IV every 3 weeks
- response rate 21% and response is better for well-differentiated STS (36%)

Vincristine, Doxorubicin, and Cyclophosphamide
- vincristine 0.7 mg/m2 IV on days 8 and 15
- doxorubicin 30 mg/m2 IV on day 1
- cyclophosphamide 100-150 mg/m2 IV on day 1
- vincristine, doxorubicin, and cyclophosphamide are repeated every 3 weeks
- prophylactic antibiotics may be required for chemotherapy-induced neutropenia

Doxorubicin and Cyclophosphamide
- doxorubicin 30 mg/m2 IV on day 1 and cyclophosphamide 150 mg/m2 IV on day 1 or PO on days 3, 4, 5, and 6
- overall response rate 73%
- response rate better for poorly differentiated rather than well-differentiated STS

OPLA-Cisplatin
- open-cell polymer lactic acid sponges containing cisplatin placed in 30 dogs with 32 incompletely resected STS
- OPLA-cisplatin is an effective treatment for incomplete resection of STS with microscopic disease
- median cisplatin dose 35.5 mg/m2
- local toxicity to OPLA-cisplatin is observed in 50% dogs with subsequent removal of the implant in 28%
- local recurrence in 31% with median time to recurrence 640 days

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63% survival rate without recurrence or metastasis
grade III STS had significantly worse prognosis

Doxorubicin Analogue (FCE 23762-methoximorpholic acid-doxorubicin)
- 20% PR with 203 day median response duration

Other
- doxorubicin and decarbazine
- gemcitabine: overall response rate 18% with median response duration 3.5 months in humans with advanced STS
- acemannan is an immunostimulant which increases tumor necrosis and inflammation with effective tumor down-staging and MST 372 days in dogs with recurrent or poor prognosis STS

RADIATION THERAPY

General Considerations
- indications: adjunctive treatment for incompletely resected STS
- adjunctive and curative-intent radiation therapy: daily (Monday-Friday) protocol with total dose between 45-57 Gy
- gross STS are considered resistant to curative-intent radiation therapy
- hyperthermia can be combined with radiation therapy to improve response rates and survival time, but effects are controversial as other studies show decreased DFI
- whole body hyperthermia does not improve response rate in comparison to local hyperthermia and may increase risk of metastatic disease

Prognosis

Radiation Therapy
- complete response rate 30%
- 43%-58% local tumor recurrence rate
- 1-year DFI at 45 Gy total dose is 48%
- 1-year DFI at 50 Gy total dose is 67% and 2-year DFI is 20%-33%
- hemangiopericytoma is more responsive than FSA and primary STS more responsive than recurrent STS

Adjunctive Radiation Therapy
- 16% local recurrence rate with median time to local recurrence 700 days to > 798 days
- median DFI 1,082 days, with:
  - 1-year DFI 71%-95%
  - 2-year DFI 60%-91%
  - 3-year DFI 57%
- MST 1,851 days, with:
  - 1-year survival rate 80%-87%
  - 2-year survival rate 72%-87%
  - 3-year survival rate 68%-81%
  - 4-year survival rate 81%
  - 5-year survival rate 75%-76%
- MST depends on site, type of STS, histologic grade, and presence of distant metastasis
- MST for oral STS 540 days and for non-oral sites 2,270 days
- MST for FSA > 914 days, MST for hemangiopericytoma 5.1 years, and MST for other STS 3.7 years
- MST for grade I and II STS > 1,461 days, and MST for grade III STS 1,241 days
- MST for dogs with metastasis 250 days

Radiation Therapy and Hyperthermia
- radiation therapy and hyperthermia improves duration of local control with no apparent increase in toxicity
- whole body hyperthermia associated with higher complication and metastatic rate than local hyperthermia
- overall response rate 65% with CR 17%, PR 48%, SD 31%, and PD 3% of 29 dogs with STS, and a 7-month median duration of response

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• 30%-45% local tumor recurrence rate
• median duration of local control for radiation therapy 350 days and radiation therapy and hyperthermia 750 days
• MST 15 months

Radiation Therapy and Chemotherapy
• curative-intent radiation therapy and chemotherapy for in 41 dogs:
• radiation therapy and chemotherapy combinations has been investigated in 41 dogs with incompletely resected STS:
  • radiation therapy protocol: 3 Gy fractions for 17 treatments and 51 Gy total dose
  • chemotherapy protocol: 10 mg/m² doxorubicin IV q 7 days
  • 18% recurrence rate with median DFI 213 days
  • 15% distant metastasis with median metastasis-free interval 276 days
  • 1-year DFI 84% and 2-4-year DFI 81%
  • 1-year survival rate 85%, 2-year survival rate 79%, and 3-4-year survival rate 72%

PROGNOSIS

General Considerations
• prognosis is usually determined by local disease control rather than distant metastasis
• 13%-32% local tumor recurrence rate after surgery alone with a median DFI 368 days
• 35%-50% local tumor recurrence rate following incomplete resection
• local tumor recurrence develops in 20% of extremity STS (54% of these were incompletely resected) and 30%
  of trunk STS (63% of these were incompletely resected)
• recurrent STS is more difficult to control than primary tumors with shorter DFI ± increased metastatic rate
• local tumor recurrence is unlikely if no recurrence is observed by 12 months postoperatively
• histologic grade and completeness of excision correlate with response to surgery
• MST 1,416 days or 3.9 years

Surgical Margins
• surgical margins is commonly cited as the most important prognostic factor for local tumor recurrence
• tumor size and location are reported as prognostic factors, but this may be related to the ability to achieve
  complete histologic resection of STS and local tumor control
• small tumors (i.e., < 5 cm) have a better prognosis than large tumors (i.e., ≥ 5 cm) for surgery or surgery and
  adjuvant radiation therapy
• STS located in superficial sites or the extremities have a better prognosis than tumors that are deep, truncal,
  invasive, or close to the spinal cord for surgery and adjuvant radiation therapy or radiation therapy alone
• ± degree of fixation to underlying tissues

Histologic Grade
• histologic grade correlates with local tumor recurrence, metastasis, and survival time
• grade I: metastatic rate 9%-13%
• grade II: metastatic rate 7%-30%
• grade III: metastatic rate 41%-50%

Tumor Type
• FSA is less responsive to surgery, radiation therapy, and surgery with adjuvant orthovoltage radiation therapy
• peripheral nerve sheath tumor site:
  • nerve root: 72% local tumor recurrence rate with a median DFI 7.5 months and MST 12 months
  • plexus: 72% local tumor recurrence rate with a median DFI 1 month and MST 5 months
• non-myxoid tumors have a worse prognosis in humans compared to myxoid sarcomas
• p53 mutation is a poor prognostic indicator

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