Four-Fraction Radiation Therapy for Macroscopic Soft Tissue Sarcomas in 16 Dogs

A retrospective study of 16 dogs with macroscopic soft tissue sarcomas was performed to evaluate response to a four-fraction radiotherapy protocol (prescribed dose of 32 Gy). Radiation was well tolerated with minimal side effects. The overall response rate was 50%, with seven partial responses and one complete response. The median time to progression was 155 days, and the median survival time was 309 days. Coarsely fractionated radiation therapy may be a reasonable palliative option for dogs with unresectable soft tissue sarcomas, although the response is relatively short-lived. J Am Anim Hosp Assoc 2008;44:100-108.

Introduction

Palliative (i.e., coarsely fractionated) radiation therapy (RT) has been used for provisional pain relief and improvement of dysfunction in both people and animals suffering from primary or metastatic neoplasia.1,2 The use of coarsely fractionated RT in veterinary medicine has principally been tailored toward management of canine osteosarcoma and melanoma, but some interest has been shown in similar protocols for temporary control of various advanced malignancies and their associated pain.1 “Definitive” RT remains the ideal approach for those animals in which long-term control may be achieved, while palliative therapy is usually reserved for dogs in which curative measures are not feasible.3-5

The radiation dose and fractionation scheme often depend on the reason for the therapy, the general health status of the dog, the volume of tissue to be treated, the relative sensitivity of the tumor type, and the critical organs or tissue that may be included in the treatment field.6 Toxicity is directly related to the tissue irradiated and increases with the overall volume of irradiated tissue, the overall delivered dose, and the dose per fraction.6 Acute side effects primarily depend on the overall radiation dose, the duration of the protocol, and the fraction size.5-7 Late radiation side effects depend particularly on fraction size and less so on overall duration.5-7 Large fraction sizes of radiation are particularly damaging to slowly dividing or nondividing normal tissue, such as connective tissue, nervous tissue, muscle, and bone.5-7 Toxicity to these late-responding tissues typically shows up >3 to 6 months after radiation, and it is dose dependent. This radiation damage is irreversible, progressive, and permanent, because the connective tissue structure and normal vasculature are compromised.6,7,9

Curative radiation protocols generally consist of relatively low doses per fraction (1.8 to 3.0 Gy) delivered daily for many weeks.6 However, it is difficult to lower the dose per fraction to ≤2.0 Gy in veterinary medicine because of the prolonged treatment time required to reach a tumoricidal dose.8 Such long treatment regimens would require excessive anesthesia (i.e., dogs are anesthetized for each fraction of radiation) and hospitalization. This has led to a compromise in which dogs are treated with a regimen with slightly higher doses per fraction.
Coarsely fractionated or “palliative” RT is typically reserved for controlling the discomfort, localized hemorrhage, and tumor progression associated with incurable cancer.\(^2,10\) Typical protocols involve large radiation doses (5 to 10 Gy) delivered as a few fractions once or twice weekly. Examples of coarse-fractionated protocols include (but are not limited to) four fractions of 8 Gy each delivered once per week, five fractions of 4 Gy given daily or once per week, and one fraction of 10 Gy or six fractions of 5 to 6 Gy delivered at a rate of one fraction per week.

Many incurable tumors are sizeable, requiring treatment of a large radiation field. Administration of higher dose fractions to a large volume of tissue increases the risk of late radiation side effects.\(^5,10,11\) Lower doses per fraction are preferred for palliative therapy, so as to preserve normal tissue structure and function.\(^5,8\) Unfortunately, some veterinary facilities have access to a radiation treatment center for only 1 to 2 days per week. Delivery of a small fraction size once per week is unlikely to lead to a durable response, because tumor cells have a significant amount of time to repair damage and to proliferate between treatments.\(^5,8\) Therefore, large doses of radiation are often delivered to optimize killing of tumor cells, with the increased risk of late radiation toxicity accepted as a part of treatment.\(^27\) Concern for clinically significant late effects can be addressed by delivering lower doses of radiation, such as 4 Gy given daily in five fractions. However, most dogs receive palliative therapy to improve quality of life, not to prolong life, and they may not live long enough to experience permanent effects.

A protocol using larger dose fractions also decreases the frequency of anesthesia. Dogs with advanced heart disease, renal insufficiency, or widespread metastasis may benefit from a course of RT that minimizes the frequency of general anesthesia, particularly if the tumor is causing only localized discomfort.\(^2,27\) Coarsely fractionated RT may offer short-term relief without compromising life expectancy, which is generally reduced by systemic disease, regardless of the treatment chosen for the cancer.\(^2,10,27\)

Soft tissue sarcomas represent a histologically diverse group of mesenchymal tumors that tend to behave similarly.\(^10\) Typical locations include the skin and subcutaneous tissues, although sarcomas can arise from any mesenchymal tissue in the body.\(^10\) These tumors are generally locally invasive and have microscopic projections that extend through the pseudocapsule, thereby predisposing to local recurrence after conservative surgical excision.\(^10,12\)

Treatment of soft tissue sarcomas has included surgery alone, RT alone, chemotherapy, or a combination of modalities.\(^13-24\) Marginal surgical resection followed by postoperative RT yields the best results, providing a median survival time of 1851 days and a time to local recurrence of >798 days.\(^24\) In some cases, this aggressive approach is not possible because of tumor location or size or because of concurrent disease. Palliative RT may offer some benefit in this setting, with the goal being to delay tumor progression and improve quality of life.

The purpose of this retrospective study was to assess the efficacy of a four-fraction palliative RT protocol in dogs with macroscopic soft tissue sarcomas.

### Materials and Methods

#### Study Animals

The RT database at the University of Wisconsin-Madison Veterinary Medical Teaching Hospital (UW-VMTH) was searched for all dogs that had been started on a course of palliative RT for macroscopic soft tissue sarcoma. Cases were included if they met the following criteria: adequate staging (including histopathological diagnosis and tumor measurements), intent to treat with four-fraction RT, and sufficient follow-up information. Medical records were reviewed for signalment, laboratory data (including complete blood count [CBC], serum biochemical profile, urinalysis, histopathological tumor diagnosis), clinical staging, pretreatment tumor volume, treatment methods (radiation protocol, overall duration of radiation, chemotherapy, surgery, and any other medications), radiation side effects, underlying reason for the owner seeking RT, owner satisfaction, and tumor response to RT.

#### Responses and Toxicities

Side effects for dogs treated after October 2001 were formally graded according to the Veterinary Radiation Therapy Oncology Group acute RT morbidity scoring scheme.\(^25\) Results were recorded for each dog throughout therapy and at follow-up with UW-VMTH. This same scoring scheme for acute and late toxicity was also retrospectively applied (based on notations within the medical record) to all dogs treated before October 2001, even though a standardized scoring scheme was not in effect at that time.

Tumor size was measured at the initial consultation, at the administration of each fraction, and at various intervals after RT had been completed. Tumor measurements were not always recorded by the same individual. Tumor volume was calculated according to the formula \(v = \pi/6(lwh)\), in which \(l\), \(w\), and \(h\) represent diameters in three mutually orthogonal planes. Individual dimensions were recorded at the time of each radiation treatment, but tumor volume was more consistently recorded during follow-up. Therefore, volume estimates were used for evaluation of response.

A “complete response” was defined as complete disappearance of all measurable tumor. A “partial response” was defined as >50% reduction in tumor volume. “No response” was defined as <50% reduction and ≤25% increase in tumor volume. Progressive disease was defined as a >25% increase in tumor volume. Overall response rate was defined as the percentage experiencing complete or partial response.

Follow-up information was obtained through rechecks at UW-VMTH, through standardized satisfaction postcards sent to owners after RT, or through telephone communication with owners and/or referring veterinarians. Postcards provided information on owner satisfaction with the RT, recovery from side effects, time to recurrence, and survival.
time. No formal recheck schedule was consistently followed, but the recommended follow-up schedule was 2 to 4 weeks after therapy and then every 2 to 3 months thereafter, unless problems arose.

The “progression-free” interval was defined as the time between the start of RT and documented progression. If the date of tumor progression was unknown, then dogs were censored from progression-free analysis at the point of last known nonprogressive follow-up. Survival times were calculated from the start of RT until documented date of death. Dogs were censored from survival analysis if their deaths were unrelated to the tumor, if they were lost to follow-up, or if a cause of death was unknown.

Statistics
The median progression-free interval and survival time were calculated using the Kaplan-Meier product-limit method.26 Response to treatment and tumor size were evaluated for their association with these outcomes. Differences in progression-free interval and survival time between groups were compared using the logrank test. A two-sided Fisher’s exact test was used to compare the likelihood of response associated with receiving or not receiving concurrent chemotherapy and larger versus smaller (than the median) tumor volume. Statistical calculations were performed using a commercial statistical software package. A P value <0.05 was considered significant in all analyses.

Results
The database included 18 dogs with soft tissue sarcoma treated with palliative RT between March 1995 and January 2002. Results of complete blood work, urinalysis, thoracic radiographs, and histopathology were available for all dogs. Additional diagnostics included computed tomography (CT) scan (n=4), abdominal ultrasound (n=5), magnetic resonance imaging (MRI) (n=1), echocardiogram (n=1), and skull (n=2) or pelvic (n=1) radiographs. Two of the 18 dogs were excluded from the study because of incomplete medical records.

Of the 16 dogs included in this study, 12 were neutered males and four were spayed females. The ages ranged from 3 to 15 years, with a median of 10 years and a mean (± standard deviation [SD]) of 9.9 (±3) years. Breeds included golden retriever (n=3), Labrador retriever (n=3), mixed-breed dog (n=3), Siberian husky (n=2), German shepherd dog (n=2), Shetland sheepdog (n=1), toy poodle (n=1), and Doberman pinscher (n=1).

Tumor Characteristics
Soft tissue sarcomas consisted of various histiotypes located in several areas of the body [see Table]. Pretreatment tumor volumes ranged from 5.65 cm³ to 1754 cm³, with a median of 81 cm³ and a mean (± SD) of 260 (±449) cm³. Records indicated that 12 of the 16 owners had sought therapy because of pet discomfort related to the sarcoma. The reason behind palliative therapy was not specifically documented in the other four cases, but medical records suggested that these four tumors were treated to slow the progression of the tumor and to alleviate presumed discomfort. In all cases, potentially curative therapy was offered to the owners. Such therapy included amputation, body wall resection, complete surgical excision, and/or definitive RT. All owners declined definitive treatment and elected palliative therapy.

Treatment Protocol
The RT protocols consisted of manual methods using single or parallel opposed fields, with a 3-cm margin surrounding the palpable edge of the tumor (if possible). Computed tomography scans were used when available to help estimate field size and depth of treatment, but true image-based computer planning was not performed. When feasible, critical structures such as eyes, nasal planum, and lungs were blocked from inclusion in the field. For appendicular sites, a narrow portion of tissue was spared to decrease the risk of radiation-induced lymphatic obstruction. The total dose of radiation prescribed to the tumor was 32 Gy to isocenter, delivered as one 8-Gy fraction on days 0, 7, 14, and 21. All fractions were administered using a cobalt teletherapy unit.a

Other Therapies
In addition to four-fraction RT, 12 dogs received other therapy before, during, or after RT [see Table]. Tumors continued to progress in all 12 dogs in the face of therapy given before RT. Three dogs had received concurrent doxorubicin/cyclophosphamide chemotherapy at standard dosages at 3-week intervals for four cycles. Medical records of these three dogs suggested that chemotherapy was administered to help improve tumor response to RT. Further therapy at the time of tumor progression consisted of piroxicam (n=3), investigational Phenstatin phosphate chemotherapy (n=1), endostatin gene therapy and genetically modified Salmonella (n=1), additional radiation (n=2), or chemotherapy (n=1).

Response to Treatment
Radiation therapy was given to 15 of the 16 dogs on days 0, 7, 14, and 21. The remaining dog (case no. 7; see Table) became clinically ill secondary to neutropenia induced by chemotherapy, so the first and second fractions of radiation were delivered 2 weeks apart. Two of the 16 dogs had achieved a partial response by the fourth radiation dose, and one dog had stable disease at that time. Radiation was well tolerated, with all dogs continuing to display normal or subjectively improved attitudes, appetites, and energy levels.

Mild, acute side effects were noted during therapy. Grades of acute toxicity were assigned prospectively to one hospitalized dog (using standardized toxicity criteria), but all other cases were graded retrospectively. Two dogs developed grade-1 skin desquamation; three dogs developed grade-2 moist desquamation; and three dogs developed grade-2 oral mucositis. All eight of these dogs were rechecked within 2.5 weeks of completion of RT, at which time all acute side effects had resolved. Four of the eight
<table>
<thead>
<tr>
<th>Dog</th>
<th>Tumor Histotype</th>
<th>Location</th>
<th>Preradiation Therapy</th>
<th>Concurrent Chemotherapy</th>
<th>Postradiation Therapy</th>
<th>Tumor Response to Radiation</th>
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<td>Stable disease</td>
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* Note: All tumors that were surgically excised had recurred by the time of radiation therapy. All postradiation treatments were instituted at the time of documented tumor progression.

† Doxil: 1 mg/kg intravenously q 3 wks
‡ Piroxicam: 0.3 mg/kg per os q 24 h
§ Radiation therapy: Two fractions of 5 Gy delivered 1 wk apart
\(\) Cyclophosphamide: 150 mg/m² intravenously q 3 wks; doxorubicin: 30 mg/m² intravenously q 3 wks
¶ Radiation therapy: Two fractions of 6.5 Gy delivered 1 wk apart
Each of the 16 dogs was evaluated at some point after therapy by a referring veterinarian, with five of the 16 dogs rechecked at 14 to 19 days after completion of therapy. Of the 16 cases, 13 were also reevaluated at the UW-VMTH at some time period between 2 weeks (four dogs) and 8 months (one dog) after treatment. Recheck evaluations were recommended at regular intervals (i.e., 2 weeks, then 1 month, then every 3 months), but few dogs were consistently returned for evaluation, and the level of follow-up varied. For example, of the 13 dogs reevaluated at UW-VMTH, one was evaluated at 2 and 4 weeks; two were evaluated at 1 month, with repeat evaluations at 2-month intervals; and one was evaluated at 3 and 5 months. All other cases were rechecked at UW-VMTH no more than once.

The overall objective response rate was 50% and included seven partial and one complete response. Three dogs experienced a 30% to 40% reduction in tumor size but did not fully meet the criteria for objective response. The remaining five dogs had static tumors that did not change measurably in size. None of the dogs developed progressive disease during the course of therapy, and eight dogs experienced stable disease for a median of 140 days.

The dog that experienced a complete response had been diagnosed with a cutaneous hemangiosarcoma located over the left ventral thorax. This dog received chemotherapy concurrent with RT. The tumor did not progress for 224 days, but the dog was euthanized at 253 days because of local recurrence and ulceration of the tumor.

Nine of the 16 owners were pleased with the clinical responses achieved through treatment, with three owners reporting significant improvement of lameness in their dogs. One owner expressed mild displeasure associated with the side effects (oral mucositis) but did not regret the decision to pursue RT. In the remaining cases, owner satisfaction was not documented.

No variables were statistically associated with response to RT. All three dogs treated with concurrent chemotherapy achieved an objective response, but this finding was not statistically significant \( (P=0.10) \), likely due to the small sample size. The small sample size also precluded the statistical evaluation of whether treatment before RT affected the response rate.

The median progression-free interval was 155 days, with a range of 72 to 460 days [see Figure]. Four dogs were censored from progression-free analysis because of lack of follow-up regarding date of documented progression. Six (48%) dogs were progression free at 6 months, and two (16%) dogs were still progression free at 1 year.

Twelve (75%) dogs were alive at 6 months, and six (37%) dogs were still alive at 12 months. The overall median survival time was 309 days, with a range of 73 to 600 days [see Figure]. Three dogs were censored from survival analysis at the time of death from causes completely unrelated to the tumor. Among these three deaths, one dog with a truncal hemangiopericytoma died acutely after collapsing; one dog treated for a forelimb hemangiopericytoma was euthanized for paraparesis and fecal incontinence; and one dog with a forelimb hemangiopericytoma died secondary to unregulated diabetes mellitus and hyperadrenocorticism.

The median survival time of the eight dogs responding to RT was 218 days, and the median survival time of dogs not responding was 416 days. This difference was not statistically significant \( (P=0.34) \). The three dogs that received concurrent doxorubicin and cyclophosphamide experienced survival times of 253 days, 309 days, and 373 days.

**Discussion**

This is the first report describing the response to a four-fraction protocol in dogs with measurable soft tissue sarcomas. The literature on coarse-fractionated RT for soft tissue sarcomas is sparse, although various reports have emerged in the past 13 years. A recent report described a coarse-fractionated protocol consisting of three 8-Gy fractions given either weekly or on days 0, 7, and 21. \(^{30}\) Fifteen dogs with either fibrosarcoma or hemangiopericytoma were treated, and 13 (87%) of the 15 dogs achieved stable disease for a median of 263 days. \(^{30}\) Only one partial response was noted in this study. Time to progression and survival time were longer in this study (263 days and 332 days, respectively) \(^{30}\) than in the authors’ study (155 days and 309 days, respectively), but this may be an artifact caused by favorable case selection in the former study and by more severe, refractory disease in this study’s population of dogs. The median tumor volume in this study was 81 cm\(^3\), while that in the previous report was 75 cm\(^3\). \(^{30}\) In addition, only five tumors in the previous report had been surgically resected, and 10 were treated solely with primary coarse-fractionated radiotherapy. \(^{30}\) Recurrent tumors may be more difficult to treat, and many of the dogs in the authors’ study had received

![Figure](https://example.com/figure.png)
other forms of treatment before RT, which is often the case with advanced malignancies.10

In another report, 16 dogs were irradiated for advanced nonskeletal tumors (including melanomas and sarcomas) using three fractions of 8 Gy each.1 The protocol was tolerated well, with quick pain relief and minimal side effects. These dogs survived for up to 557 days after treatment.1

In the authors’ study, 50% of dogs responded to therapy, and dogs remained progression free for a median of approximately 5 months. Limb function was definitively improved after RT in three dogs; two of these dogs were partial responders, but the third dog did not have a measurable response. All dogs tolerated RT well, with minimal and acceptable acute side effects. Late effects were not noted in any of the 16 dogs. However, the median survival time was 10 months, and late effects may not have become clinically apparent within that time period.

The authors chose a protocol consisting of 8-Gy fractions administered once weekly, based on a recommended fractional dose of 8 Gy for optimal palliation of bone metastasis in people.28,29 Use of this fractionation scheme has been standard practice at UW-VMTH, even though a 0-7-21-day protocol has been used in previous studies.3,30 A dose of 8 Gy is estimated to kill approximately 70% to 80% of the tumor population.27

Radiation protocols can be compared using a formula known as the “biological equivalent dose” (BED), which estimates effective doses to tissues.5 Assuming α/β ratios of 10 for acute effects and 3 for late effects, the BED for the authors’ four-fraction protocol is 57.6 Gy10 for acute effects and 117.3 Gy3 for late effects. By comparison, using 8-Gy fractions in the published 0-7-21-day protocol for advanced malignancies and soft tissue sarcomas yields BEDs of 43.2 Gy10 for acute effects and 88 Gy3 for late effects.1,30 These findings suggest that the authors’ four-fraction protocol may have greater efficacy against acutely responding tissue such as tumor, but that late-responding tissues will also be more affected (i.e., greater probability of late side effects).

Coarsely fractionated protocols can certainly cause significant late tissue damage and (if used inappropriately) can eventually impact quality of life during a durable response.5,7 However, some radiation oncologists may be less concerned with late effects when dealing with palliative therapy, because dogs undergoing such treatment do not live long enough to experience late radiation effects. None of the dogs in this study suffered any reported late effects (even given the higher effective dose for late-responding tissues), which was most likely a result of the relatively short survival time. The incidence of late effects possibly would have been higher if the dogs had survived longer.

Applying the BED formula to a published definitive-radiation protocol of 19 fractions of 3 Gy each yields effective doses of 74 Gy10 for acute effects and 114 Gy3 for late effects.24 This definitive protocol, which is prescribed to cure microscopic disease, yields a higher effective dose for acute effects (tumor) and a lower BED for late effects than the protocol the authors used to treat bulky, nonresectable soft tissue sarcomas. This highlights the fact that coarse-fractionated protocols are not meant to replace definitive, protracted RT because of the potential negative impact on normal structures associated with palliative, coarse-fractionated procedures.

Large soft tissue sarcomas can cause significant discomfort and impairment in normal function. Analgesics are often used to maintain quality of life when other therapeutic options are not feasible. Curative surgery with or without RT may not be feasible because of tumor size and location. Alternative management methods for nonresectable soft tissue sarcomas are needed. Preoperative, definitive radiation protocols may prove beneficial by shrinking the tumor to a resectable volume. Additionally, amputation may be curative for dogs with low- or intermediate-grade soft tissue sarcomas of the distal limb.

The use of chemotherapy for soft tissue sarcoma is somewhat controversial, because chemotherapy in combination with radiation has not been shown to definitively improve response or survival, although it may provide palliation in the case of measurable tumors.10,16,31 The use of chemotherapy in combination with palliative RT has not been assessed but may potentially delay onset of systemic disease and improve/maintain quality of life in the case of metastatic tumors. An alternative view is that chemotherapy has the potential to make animals ill, and it may not significantly impact the disease process underlying patient discomfort.

Limitations of this study included the small sample size, the lack of a control group, the observational (i.e., nonrandomized) and retrospective design, and variable use of adjuvant therapies. Only 16 dogs were evaluated, and these could not be compared to a similar group of dogs that did not receive RT. Bias (e.g., confounding or selection bias) is also a potential problem in any observational study (especially a retrospective one), although it is difficult to determine if such bias actually occurred. Owners of dogs in profound discomfort with advanced disease may be less likely to opt for RT, and it is possible that the dogs in the authors’ study population were healthier than the average dog with soft tissue sarcoma. In other instances, definitive treatment of operable tumors may be declined for various reasons. In these cases, coarsely fractionated RT serves as palliative therapy for dogs experiencing poor quality of life, rather than as a true substitute for definitive treatment.

It is not known whether the 16 dogs in this study would have survived as long as they did without palliative therapy. However, early euthanasia was a real possibility in these cases, given that most (11 of 16) owners sought treatment for deteriorating quality of life. The retrospective nature of this study made it difficult to adequately evaluate pain relief and return to function among treated dogs, given that tumor size and response to therapy were documented more thoroughly than resolution of discomfort.

The authors also may not have captured the full range of improvement among treated dogs. Some tumors can take months to shrink, so it is possible that tumor volume may have continued to decrease even among dogs that did not
achieve an objective response during the study and follow-
up periods. Tumor volume was not consistently measured
during reevaluation, but it is clear from time-to-progression
data that any additional shrinkage was temporary.

As with any retrospective study, the authors did not have
control over numerous treatment-related variables, frequen-
cy of reevaluation, etc. One source of concern is the fact that
most dogs were treated with a wide variety of additional
therapies before or after RT. However, only three dogs had
concurrent chemotherapy that might have affected assess-
ment of response to RT. While variable chemotherapeutic
regimens, investigational agents, and prior surgical exci-
sions were performed before RT, a 50% response rate was
still achieved.

It is impossible to know with certainty whether pretreat-
ment had a substantive impact on response or progression-
free interval. Various treatment regimens, such as gene
therapy or prior surgery, certainly may have altered tumor
blood supply or gene expression. Such concurrent treat-
ments may have also modulated “bystander effects” associ-
ated with RT, thereby modifying inherent tumor response to
ionizing radiation. Chemotherapy may act in conjunction
with RT, so it is also conceivable that dogs receiving
chemotherapy had improved responses to RT. In this regard,
there was not significant, so it may have been a chance
occurrence. However, it should be noted that four of the
nonresponders had tumors located on the extremities.
Perhaps tumors on the extremities were better compensated
for than tumors located on the trunk or within the oral cav-
ity. Alternatively, such tumors possibly were innately less
proliferative than other tumors.

Conclusion
Aggressive local therapy remains the standard of care for
treatment of soft tissue sarcomas and often involves a com-
bination of surgery and definitive RT. However, results of
this study support the use of coarsely fractionated RT as a
viable therapeutic option for soft tissue sarcomas, if defini-
tive treatment (e.g., surgery with or without curative RT) is
not elected or is not expected to improve local control.
Furthermore, RT delivered as four weekly fractions may be
attractive to some owners because of the fewer number of
visits and less time required for hospitalization.

Such short-course, high-dose protocols result in a rela-
tively high risk for late radiation side effects. This fact
should be considered and explained to owners, particularly
in cases where animals may be better served by protocols
intended to provide a cure. However, clearly nonresectable,
large, bulky tumors may respond well to coarse-fractionat-
ed RT over the short term. The coarse-fraction protocol was
well tolerated by all dogs in this study and may offer an
opportunity for temporary relief of pain and return to func-
tion. The ideal protocol to achieve good local control and
amelioration of clinical signs has yet to be determined.

Footnotes
1. Theratron 780; Atomic Energy of Canada, Kanata, Ontario, K2K
1X8, Canada
2. Prism 4.0b; GraphPad Software, San Diego, CA 92130

References
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Lumbosacral Intervertebral Disk Disease in Six Cats

Medical records of six cats diagnosed with lumbosacral intervertebral disk disease were reviewed. Clinical signs included reluctance to jump, low tail carriage, elimination outside the litter box, reluctance to ambulate, pelvic-limb paresis, urinary incontinence, and constipation. All cats had lumbosacral hyperpathia on palpation. Computed tomography in four cats revealed evidence of extradural spinal cord compression at the seventh lumbar (L₇) to first sacral (S₁) vertebral interspace. Compression was confirmed via myelography in three of these four cats, with confirmation in the fourth cat at the time of decompressive laminectomy. Each of the six cats underwent dorsal decompressive laminectomy at the L₇ to S₁ interspace. Postoperative clinical follow-up lasted 3 to 35 months, with most cats having excellent outcomes. J Am Anim Hosp Assoc 2008;44:109-115.

Introduction

Intervertebral disk disease (IVDD) within the lumbosacral spine is a frequently reported and documented clinical disease syndrome in dogs, but little is known about lumbosacral IVDD in cats. Disk degeneration and protrusion occur commonly in cats and are routine incidental findings at necropsy.¹,² However, IVDD in cats is not usually accompanied by recognized clinical signs.¹,²

To the authors’ knowledge, only one clinical case of feline lumbosacral IVDD has been reported.¹² Therefore, this retrospective study was performed to evaluate clinical signs and surgical outcomes in cats diagnosed with lumbosacral IVDD to further understand this disease process in domestic cats.

Materials and Methods

Medical records of feline cases of lumbosacral IVDD that were referred to California Veterinary Specialists between October 2002 and October 2006 were reviewed. Inclusion criteria consisted of 1) diagnosis of lumbosacral IVDD based on the results of myelography, computed tomography (CT), or confirmation at the time of surgery and 2) subsequent lumbosacral decompression. Age, sex, breed, body weight, clinical history, indoor/outdoor status, presenting clinical signs, cerebrospinal fluid analysis, radiographic findings, surgical findings, and outcome for each cat were recorded if available. Follow-up surveys were administered to the clients of all cases, and residual clinical signs were recorded.

All cases were assessed for degree of “functional recovery,” which was based on regaining the ability to walk, fecal and urinary continence, and absence of persistent back pain.⁴ Recovery was rated “excellent” if the owner felt that the cat had complete resolution of lumbosacral hyperpathia, with appropriate ambulation and elimination. Recovery was rated “good” if clinical signs were improved but mild residual lumbosacral hyperpathia was seen. Recovery was rated “fair” if significant clinical signs persisted, but quality of life was still acceptable. Recovery was
“poor” if clinical signs did not resolve and quality of life was unacceptable.

For the purpose of the current study, Hansen’s type I disk disease was defined as disk extrusion into the spinal canal that causes a focal compressive myelopathy. Hansen’s type II disk disease included protrusion of disk material within an intact annulus, resulting in a compressive myelopathy. Spinal hyperpathia was defined as an unpleasant, painful response to a noxious stimulus (especially if repeated). Such a response is characterized by delay, overreaction, and after-sensation.

Results

Out of a total of 11,151 cats seen within the study time frame, six cats were diagnosed with lumbosacral IVDD, suggesting a 0.05% incidence in the authors’ hospital population. Descriptive characteristics for the six cases are presented in Table 1. The cases were equally divided between spayed females and castrated males, with domestic shorthair (DSH) being the most common breed. The mean age was 12.6 years (median 12 years), and the mean body weight was 6.5 kg [Table 1]. All six cats were kept strictly indoors.

The most common signs from the clinical histories were reluctance to jump, which was observed in all cats, and low tail carriage, which was seen in three cats [Table 2]. All cats were ambulatory on presentation and had significant pain when direct digital pressure was applied to the lumbosacral region. All five cats with a tail had pain on tail hyperextension (hyperextension was not possible in the Manx). Digital rectal evaluation was not performed in any conscious cat. Significant ancillary findings included severe bilateral stifle osteoarthritis, diabetes mellitus, and chronic renal failure (case no. 1); bilateral medially luxating patellae (case no. 4); and obesity, a ruptured cranial cruciate ligament, and cystic calculi (case no. 6).

Cerebrospinal fluid was collected from the cerebellomedullary cistern in three of the six cats; all cell counts and protein concentrations were within the reference ranges. The CT scans, which were performed in four cats, did not reveal any articular process thickening or sclerosis. Two of the four CT scans suggested a ventral compressive lesion of the cauda equina [Figures 1, 2]. The CT scan of case no. 3 revealed lumbosacral caudal malformation and dural malformation, which were confirmed by myelography.

The CT scan for case no. 4 revealed stenosis of the spinal canal within a lumbosacral transitional vertebra at the seventh lumbar (L7) to first sacral (S1) interspace [Figure 3]. Survey spinal radiographs of this cat confirmed that a transitional lumbosacral vertebra was incompletely fused to the remainder of the sacrum [Figure 4]. Myelography confirmed mild ventral compression at the L7 transitional lumbar sacral vertebra [Figure 5].

Dorsal decompressive laminectomies were successfully performed at the L7 to S1 interspace in all cats. Case no. 4 also underwent right-sided medial patellar stabilization during the same anesthetic/surgical period. One cat had evidence of extruded disk material within the spinal canal, consistent with Hansen’s type I disk disease. Five cats had no obvious disk extrusion, but one of these had a Hansen’s type II disk protrusion.

A preoperative dose of methylprednisolone sodium succinate (30 mg/kg) was administered intravenously to each cat at the start of the surgical procedure. No glucocorticosteroids were administered in the postoperative period.
### Table 1

**Clinical Findings in Six Cats With Lumbosacral Intervertebral Disk Disease**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Breed†</th>
<th>Weight (kg)</th>
<th>Clinical Signs</th>
<th>Site‡</th>
<th>Diagnostics§</th>
<th>Management</th>
<th>Follow-up (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>CM</td>
<td>Abyssinian</td>
<td>4.5</td>
<td>Reluctance to jump, pelvic-limb paresis</td>
<td>L₇-S₁</td>
<td>R</td>
<td>Surgery</td>
<td>9</td>
<td>Fair</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>CM</td>
<td>DSH</td>
<td>6.8</td>
<td>Reluctance to jump, spinal hyperpathia</td>
<td>L₇-S₁</td>
<td>R, M, CSF</td>
<td>Surgery</td>
<td>35</td>
<td>Excellent</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>SF</td>
<td>Manx</td>
<td>4.7</td>
<td>Urinary incontinence, constipation</td>
<td>L₇-S₁</td>
<td>R, M, CT, CSF</td>
<td>Surgery, cystostomy tube</td>
<td>23</td>
<td>Fair</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>SF</td>
<td>DSH</td>
<td>6.3</td>
<td>Straining to defecate, low tail carriage</td>
<td>L₇-S₁</td>
<td>R, M, CT, CSF</td>
<td>Surgery, patellar stabilization</td>
<td>15</td>
<td>Excellent</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>SF</td>
<td>DLH</td>
<td>6.5</td>
<td>Reluctance to jump, low tail carriage</td>
<td>L₇-S₁</td>
<td>CT</td>
<td>Surgery</td>
<td>3.5</td>
<td>Excellent</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>CM</td>
<td>DSH</td>
<td>10.4</td>
<td>Reluctance to ambulate, low tail carriage</td>
<td>L₇-S₁</td>
<td>CT</td>
<td>Surgery</td>
<td>3</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

* CM=castrated male; SF=spayed female
† DSH=domestic shorthair; DLH=domestic longhair
‡ L₇=seventh lumbar vertebra; S₁=first sacral vertebra
§ R=survey radiographs; M=myelogram; CSF=cerebrospinal fluid analysis; CT=computed tomography
Postoperative follow-up ranged from 3 to 35 months. Clinical signs were markedly improved within 2 weeks in four cats. Case no. 1 showed a slight improvement but had continued urine retention that may have been caused by an unrelated underlying disease process. Case no. 3 continued to have urinary incontinence, so a permanent cystostomy tube was placed during a later surgical procedure. Owner survey responses revealed that the outcomes were “excellent” in four cats and only “fair” in two cats.

**Discussion**

Little information has been published on IVDD in cats. To the authors’ knowledge, only 30 cats with clinical IVDD have been reported in the veterinary literature, with only a single case report of lumbar IVDD. These 30 cats had a total of 32 localized lesions [Table 3], because two cats had evidence of compression at both the 13th thoracic (T13) to first lumbar (L1) vertebral interspace and the fourth lumbar (L4) to fifth lumbar (L5) vertebral interspace. 

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clinical Histories</th>
<th>Duration (mo)</th>
<th>Resolution After Surgery</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic renal failure</td>
<td>24</td>
<td>None</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Bilateral stifle osteoarthritis</td>
<td>17</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weak in hind limbs</td>
<td>12</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hind-limb muscle atrophy</td>
<td>12</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unwilling to jump</td>
<td>8</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine retention</td>
<td>6</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Unwilling to jump</td>
<td>6</td>
<td>Improved</td>
<td>N/A*</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hiding</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hind-limb lameness</td>
<td>1</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Recurrent constipation</td>
<td>1</td>
<td>Improved</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unwilling to jump</td>
<td>1</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bilateral medial patellar luxation</td>
<td>Unknown</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Unwilling to jump</td>
<td>3</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carrying tail low</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Straining to defecate</td>
<td>1</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Fell 12 feet 7 years previously</td>
<td>6</td>
<td>Complete</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Unwilling to jump</td>
<td>6</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased tail movement</td>
<td>4</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unwilling to walk</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Right CCL rupture†</td>
<td>2</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Difficulty sitting and squatting</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unwilling to walk</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unwilling to jump</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carrying tail low</td>
<td>2</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulty getting into litter box</td>
<td>1</td>
<td>Complete</td>
<td></td>
</tr>
</tbody>
</table>

* N/A = not applicable
† CCL = cranial cruciate ligament
interspace. Most (23) of these cats were affected in the thoracic or lumbar spine and underwent hemilaminectomy, dorsal laminectomy, fenestration, or durotomy. Clinical outcome data were available for 20 of these 23 cats, with 18 showing postoperative improvement.

Clinically significant IVDD has been reported in cats ranging in age from 1.5 to 17 years, with a mean age of 7 years. The cats in this study were substantially older (mean 12.6 years), although still within the range reported in the literature. Chondrodystrophic breeds of dogs suffer from disk degeneration at an early age, whereas IVDD in cats appears to be a condition of middle-aged animals.

In one case report, a 5-year-old DSH presented with acute hemiparesis and Horner’s syndrome. Magnetic resonance imaging (MRI) revealed left-sided dorsal displacement of the spinal cord at the third cervical (C₃) to fourth cervical (C₄) vertebral interspace. The presumptive diagnosis was focal spinal cord edema with intervertebral disk extrusion. With conservative treatment, this cat gradually improved over 6 months.

A retrospective study evaluated IVDD in six cats. Radiographic studies confirmed narrowed disk spaces, mineralized disks, and one or more extradural compressive lesions in each cat. All intervertebral disk extrusions were in the thoracolumbar spine. Hemilaminectomy was performed in all cats, and the removed extradural material was confirmed as coming from degenerative disks. Neurological recovery was good to excellent in five (83%) of the six cats. It was concluded that IVDD in cats has many similarities to IVDD in dogs, and healthy cats with acute disk extrusion respond well to decompressive surgery.

A retrospective study evaluated IVDD in 10 cats diagnosed over an 11-year period. All disk herniations occurred in the thoracolumbar spine, with an increased incidence at the L₄ to L₅ vertebral interspace. Eight cats had Hansen’s type I disk disease, and two cats had Hansen’s type II disk disease. Nine cats had radiographic imaging, which consisted of myelography (in eight cats), CT (in three cats), or both (in two cats). The 10th cat was diagnosed at necropsy after euthanasia for clinical signs. Seven cats had been treated with corticosteroids before referral. Hemilaminectomy was performed on seven cats, of which six had extruded disk material in the spinal canal, and one had mild extradural compression over a narrowed disk space. Two cats had minimal compression on myelography and improving clinical signs, so they were conservatively managed with strict confinement for 4 weeks. Follow-up in seven cats revealed that recovery was good in one conservatively managed cat but poor in the other one, which never regained urinary or fecal continence. Recovery was good to excellent in four cats.

### Table 3

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>No. of Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₃-C₄</td>
<td>1</td>
</tr>
<tr>
<td>C₅-C₆</td>
<td>2</td>
</tr>
<tr>
<td>T₉-T₁₀</td>
<td>1</td>
</tr>
<tr>
<td>T₁₁-T₁₂</td>
<td>1</td>
</tr>
<tr>
<td>T₁₁-L₁</td>
<td>1</td>
</tr>
<tr>
<td>T₁₂-T₁₃</td>
<td>2</td>
</tr>
<tr>
<td>T₁₃-L₁</td>
<td>7</td>
</tr>
<tr>
<td>L₁-L₂</td>
<td>2</td>
</tr>
<tr>
<td>L₂-L₃</td>
<td>1</td>
</tr>
<tr>
<td>L₄-L₅</td>
<td>7</td>
</tr>
<tr>
<td>L₄-L₆</td>
<td>1</td>
</tr>
<tr>
<td>L₅-L₆</td>
<td>3</td>
</tr>
<tr>
<td>L₆-L₇</td>
<td>2</td>
</tr>
<tr>
<td>L₇-S₁</td>
<td>1</td>
</tr>
</tbody>
</table>
undergoing surgery, but it was only fair in one ambulatory cat because of fecal and urinary incontinence.\textsuperscript{9}

Type I disk disease has been reported to occur more commonly in the thoracolumbar region of cats, which is consistent with findings in dogs.\textsuperscript{9} In the authors’ study, only one cat had a type I IVDD, while five cats had type II disease. The higher proportion of type II lumbosacral IVDD in the cats of this study is consistent with that of lumbosacral IVDD in dogs.

The single case of lumbosacral IVDD reported in the literature involved an 8-year-old, castrated male DSH.\textsuperscript{12} The cat presented with a 2-day history of back pain, flaccid tail, and urinary and fecal incontinence. Myelography, CT, and an epidurogram revealed an L\textsubscript{7} to S\textsubscript{1} extradural lesion. Exploratory surgery and histopathology confirmed a Hansen’s type II disk protrusion. The cat regained neurological function by 6 weeks after surgery.

In dogs, the most common clinical presentation of lumbosacral disease is degenerative lumbosacral stenosis (DLSS) with protrusion of a Hansen’s type II disk.\textsuperscript{13} This occurs most commonly in middle-aged and medium- to large-breed dogs, especially German shepherds.\textsuperscript{12-14} Causes of lumbosacral IVDD in dogs include thickening of the dorsal annulus, mechanical instability of the lumbosacral junction, osteophyte formation within the spinal canal, thickening of the articular facet joint capsule, thickening of the interarcuate ligament, and transitional vertebrae.\textsuperscript{13} Lumbosacral hyperpathia is the most consistent clinical finding, and signs can be acute or chronic. Diagnosis of DLSS may be difficult, and IVDD can be easily confused with chronic orthopedic conditions. The diagnostic evaluation includes general, orthopedic, and neurological examinations, followed by radiographs and advanced imaging techniques such as myelography, discography, epidurography, CT, and MRI. If a lesion is not demonstrated by diagnostic imaging, exploratory surgery may be indicated.

In a study of 131 dogs with DLSS treated by dorsal laminectomy with fenestration, 56\% were German shepherds, with a 2:1 male:female ratio.\textsuperscript{14} The most common clinical signs were 1) pain on hyperextension of the tail or hind limbs (98\%); 2) reluctance or pain when jumping, rising from a prone position, or climbing stairs (92\%); and 3) lumbosacral pain (85\%) and unwillingness to perform extensive physical activity because of pain or stiffness (85\%). Overall, 79\% of dogs returned to normal after surgery, and 93\% showed clinical improvement within the follow-up period (26±17 months). The rate of recurrence based on owner observation or clinical examination was 18\%.\textsuperscript{14}

The above results are similar to those reported in another study of 69 dogs with DLSS that underwent dorsal laminectomy. The male:female ratio was 2.6:1, with German shepherds as the most common breed (27\% of cases).\textsuperscript{15} Clinical signs were also similar and included lower lumbar pain (77\%); difficulty jumping, climbing, rising, or sitting (53\%); hind-limb lameness (38\%); tail paralysis (16\%); and urinary or fecal incontinence (16\%). Neurological examination revealed pain on palpation or hyperextension of the lumbosacral junction (91\%) and conscious proprioceptive deficits (39\%). The outcomes after surgeries were again good, with excellent results reported for 78\% of dogs during follow-up (38±22 months).\textsuperscript{15}

As with DLSS of dogs, diagnosis of cats with IVDD may be difficult, and IVDD can be easily confused with chronic orthopedic conditions. Clinical histories and physical findings for the cats in the authors’ study were similar to those reported for dogs with DLSS. All cats in the authors’ study were reluctant to jump, with low tail carriage seen in three cats and reluctance to ambulate in two cats. All cats had pain when the lumbosacral region was palpated, and all (except the Manx) had pain on tail hyperextension. Hansen’s type II disease predominated in this study, as it does in dogs, and recoveries after dorsal decompressive laminectomies were good to excellent in most cats. The authors have not to date noted any recurrence of clinical signs in the six cats that were treated for IVDD, which is consistent with the other literature reports of IVDD in cats. Recurrence has been documented in dogs.\textsuperscript{16}

In contrast to dogs with DLSS reported in the literature, the cats in the authors’ study were older, with a mean age of 12.6 years. No specific breed or sex predilection was noted. One of the cats in this study had evidence of a Hansen’s type I disk extrusion at the time of surgery, and one had urinary retention. The persistent, postoperative urinary incontinence in the Manx was probably associated with sacrocaudal dysgenesis, which is inherited in this breed as an autosomal dominant trait with varying degrees of sacral or lumbar deformities.\textsuperscript{17}

Sacrocaudal dysgenesis and associated malformations have been recognized in most breeds of cats and are especially common in tailless breeds. Many tailless cats do not have neurological deficits, and sacral/caudal deformities are usually reported as incidental radiographic findings.\textsuperscript{17} Clinical findings depend on the degree of cauda equina or spinal cord malformation. Signs include paraparesis, paraplegia, megacolon, atomic bladder, absent anal reflex, urinary and fecal incontinence, and perineal analgesia. Diagnosis is made based on clinical signs, radiography, myelography, and CT scan. Bladder expressions and fecal softeners can be used to manage mildly affected cases, but recurrent urinary tract infections, megacolon, and chronic constipation are common persistent problems. Treatment is ineffective in severely affected cats.\textsuperscript{17}

Three cats in the authors’ study had preexisting orthopedic disease:

1) The cat with concurrent cranial cruciate ligament rupture was obese and had cystic calculi. The stifle injury was not addressed during follow-up, and this cat had residual postoperative lameness.

2) The cat with medially luxating patellae had stabilization of one patella performed during the same anesthetic/surgical episode as the dorsal decompressive laminectomy. Clinical signs resolved completely, and
the contralateral patella was stabilized 6 weeks after the first surgery.

3) The cat with a history of chronic renal failure and bilateral stifle degenerative joint disease (DJD) showed improvement of lumbosacral clinical signs after surgery, but urinary retention persisted. The DJD was not treated. Nine months after surgery, this cat died from renal disease and congestive heart failure.

It is not known if the orthopedic disease was a factor in the development of lumbosacral IVDD or if IVDD was a sequela of orthopedic conditions in this patient population.

Limitations of this study include its retrospective nature and the lack of consistent diagnostic imaging data for all cases. Computed tomographic scans were performed in four of the cases, but lumbosacral lesions can be difficult to visualize with CT. Magnetic resonance imaging may have improved the authors’ diagnostic capabilities, but recent research on DLSS in dogs suggests a high degree of agreement between CT and MRI. Therefore, the authors feel that CT imaging was an acceptable diagnostic modality. Furthermore, the recent canine study showed only a slight to fair agreement between diagnostic imaging and surgical findings.

A further limitation of the study was the small sample size. However, this is consistent with the low numbers of feline IVDD cases that have been reported previously. All of the cats in this study underwent surgical decompression; therefore, no conservatively managed cases were available for comparison.

Conclusion

Until recently, lumbosacral IVDD in cats has been infrequently recognized and reported, with only 30 reported cases of feline IVDD. With one exception, all cases in this series had long-standing clinical histories and clinical signs attributable to lumbosacral disease. Therefore, the authors feel that the clinical signs correlated well with their diagnostic and surgical findings. Furthermore, all cats had clinical resolution or were significantly improved after lumbosacral decompression, regardless of concurrent disease and advanced age.

Subtle signs such as reluctance to jump and low tail carriage may be overlooked as early indicators of IVDD in cats. Therefore, the incidence of lumbosacral IVDD in cats may be higher than previously recognized. Lumbosacral IVDD should be considered as a differential diagnosis in all cats having caudal lumbar pain or pain on tail hyperextension.

Footnotes

a Solu-Medrol; Pharmacia, Kalamazoo, MI 49001

References

Palliation of Clinical Signs in 48 Dogs With Nasal Carcinomas Treated With Coarse-fraction Radiation Therapy

Data from 48 dogs with nasal carcinomas treated with palliative radiation therapy (PRT) were retrospectively reviewed. Factors potentially influencing resolution of clinical signs and survival after PRT were evaluated. Clinical signs completely resolved in 66% of dogs for a median of 120 days. The overall median survival time was 146 days. Duration of response to PRT was shorter in dogs that had clinical signs for <90 days before PRT. Survival times were shorter in dogs that had partial or no resolution of clinical signs after PRT than in dogs that had complete resolution of clinical signs. J Am Anim Hosp Assoc 2008;44:116-123.

Introduction

Malignant neoplasms of the nasal cavity and paranasal sinuses cause local soft-tissue and bony destruction, resulting in clinical signs such as epistaxis, sneezing, facial deformity, and upper-airway dyspnea.1-12 Without therapy, progression is fairly rapid. The reported median survival times for 16 dogs with various intranasal neoplasms were 10.5 weeks from the initial onset of clinical signs and 3.5 weeks from presentation to a veterinary facility.4 In a recent study of 139 dogs with untreated nasal carcinomas, survival times ranged from 7 to 1114 days (median 95 days).12

Treatment options for dogs with nasal carcinoma include surgery, external-beam radiation therapy (RT), brachytherapy, immunotherapy, and chemotherapy.1-15 External-beam RT has become the treatment of choice for nasal tumors, because historical evidence suggests that surgery

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or chemotherapy alone rarely provides long-term tumor control. Unfortunately, even with treatment, most dogs with nasal carcinomas are eventually euthanized because of local disease progression and worsening of clinical signs.

Nasal tumors are most often seen in older dogs (median age approximately 10 years), and many affected dogs have concurrent diseases that contribute to overall morbidity. Concurrent illness also makes decisions about treatment increasingly difficult for both the owner and the veterinary oncologist. In some cases, advanced local disease or the presence of metastasis makes the clinician hesitant to recommend a definitive course of RT because of the potential for adverse effects in a dog with a poor long-term prognosis. For these dogs, a palliative course of RT may be considered to minimize hospitalization, the number of anesthetic episodes, and adverse effects normally associated with definitive RT.

The goal of palliative radiation therapy (PRT) is to improve quality of life while minimizing treatment-associated morbidity. Radiation therapy can decrease pain associated with bony lysis, inflammation, or tissue compression caused by tumors. Improvement of clinical signs may also prolong life, although this is not the primary goal of PRT.

Information regarding use of PRT protocols in dogs with sinonasal cancer is lacking. The purpose of the current study was to evaluate the clinical characteristics and outcomes of dogs with nasal carcinomas treated with PRT.

Materials and Methods

Criteria for Case Selection

Patient records from eight contributing institutions were reviewed for the period between 1996 and 2005. Dogs that had histologically confirmed nasal or paranasal carcinomas treated with PRT were included in the study, as well as those that had been treated with nonsteroidal antiinflammatory drugs (NSAIDs), steroids, or antibiotics before or concurrently with PRT. Dogs that had inadequate follow-up or that had received previous RT, chemotherapy, or surgery were excluded.

Case Data

Data abstracted from medical records included 1) patient characteristics, such as age, weight, breed, presence of clinical signs, duration of clinical signs, and treatments before diagnosis; 2) diagnostic information, such as results of imaging methods and histopathological diagnosis; 3) treatment data, including reason for PRT, radiation source, dose per fraction, number of fractions administered, schedule for RT, and description of the radiation treatment field; and 4) follow-up data, including adverse effects associated with PRT, medications administered during and after completion of PRT, response to PRT (including resolution of clinical signs and response duration), survival time, and cause of death. Follow-up information was obtained from existing records or telephone interviews with the referring veterinarian and/or owner.

Information was obtained, when available, on the results of staging procedures, including cytological examination of regional lymph nodes, radiography of the thorax and abdomen, and ultrasonography of the abdomen. Systemic staging was performed according to clinician preference. Clinical tumor staging was based on results of computed tomography (CT) or magnetic resonance imaging (MRI), with tumors categorized according to a published classification system for sinonasal tumors. Clinical staging was not assessed when CT or MRI findings were unavailable.

Statistical Analysis

Duration of clinical signs before PRT was defined as the interval between the onset of clinical signs (as reported in the medical record) and the initiation of radiotherapy. For dogs in which clinical signs resolved completely, response duration was defined as the interval between the final dose of PRT and recurrence of clinical signs. Dogs in which clinical signs did not resolve completely were not included in analysis of response duration. Survival time was defined as the time from the end of PRT until death from any cause. Dogs that were free of clinical signs or alive at the last follow-up were included in analyses until the last day of follow-up, and then they were censored. Additionally, dogs that received a second course of PRT were censored from survival analyses at the time the second course was begun.

Risk factors were analyzed as possible predictors of response to PRT or survival. These risk factors included duration of clinical signs before the initiation of PRT (<90 days versus ≥90 days), Adams’ stage (stages 1 and 2 versus stages 3 and 4), total radiation dose (<24 Gy versus ≥24 Gy), dose per fraction (<8 Gy versus ≥8 Gy), complete resolution of clinical signs during or after PRT (yes versus no), and use of antiinflammatories (NSAIDs or steroids) with or without antibiotics during and after PRT (yes versus no).

Chi-square and Fisher’s exact tests were used to screen categorical data for associations with complete resolution of clinical signs. The Kaplan-Meier product-limit method was used to estimate response duration and survival curves for each potential risk factor. These curves were then compared using the logrank test for censored data. Multivariable survival analysis using the Cox proportional-hazards method was performed to evaluate the joint effects of potential risk factors on response duration and survival. Variables with $P$ values ≤0.05 in the univariable analysis were initially considered in the multivariable analysis, with stepwise backward elimination used for final model selection. In the final analysis, $P$ values ≤0.05 were considered significant.

Results

Medical records of 65 dogs with nasal carcinomas were retrospectively evaluated for inclusion in the study. Ten dogs that had inadequate follow-up were excluded, as were seven dogs that had received chemotherapy concurrent with or after PRT. Of the remaining 48 dogs, 23 were male (19 castrated) and 25 were female (24 spayed). Weights ranged from 4 to 50 kg (median 24 kg, mean 24 kg). Age ranged
The duration of clinical signs before evaluation was known for 44 dogs and ranged from 7 to 730 days (median 90 days, mean 142 days). Clinical signs included epistaxis (n=40, 83%), sneezing (n=31, 65%), nasal discharge (n=26, 54%), facial deformity (n=19, 40%), upper-airway dyspnea (n=16, 33%), and ocular abnormalities (n=13, 27%). Most dogs had more than one clinical sign at presentation. Ocular abnormalities included decreased ocular retropulsion, third eyelid protrusion, exophthalmos, and epiphora. One dog with minimal signs related to the nasal cavity was presented for evaluation of ataxia, acute-onset blindness, and seizures.

Of the 39 (81%) dogs treated empirically for nasal signs before sinonasal neoplasia was diagnosed, 11 (28%) had partial or complete resolution of signs after treatment. Dogs were treated with NSAIDs (n=11), steroids (n=16), antibiotics (n=23), or combinations of these medications (n=10) before PRT. In most cases, the resolution of clinical signs resulting from these treatments lasted <1 month.

In 11 (23%) dogs, mandibular lymph nodes ipsilateral to the tumor were aspirated. The records did not indicate whether these lymph nodes were enlarged at diagnosis, but no dogs had cytological evidence of lymph node metastasis. Thoracic radiographs were taken in 47 (98%) dogs and were unremarkable except for a presumed primary lung tumor seen in one dog.

Information on tumor staging was available for 42 cases. Stages were based on retrospective evaluation of CT (n=41) or MRI (n=1) reports, and they were categorized as T1 (n=4), T2 (n=6), T3 (n=10), or T4 (n=22). 1

The reasons for treating patients with PRT (as opposed to definitive therapy) were documented in 40 (83%) cases. In 14 (35%) dogs, the extent of local disease was listed as the cause for recommending PRT. In 24 (60%) cases, owners requested PRT because of concerns about cost, potential for toxicity, or travel/hospitalization associated with definitive RT. In two (5%) dogs, PRT was recommended because of concurrent diseases, including cardiac arrhythmias and the presence of a presumed primary lung tumor.

Dogs were treated with a course of PRT using standard protocols of each institution. After general anesthesia was induced, dogs were treated with megavoltage radiation using either a linear accelerator (n=32) or a Cobalt-60 teletherapy unit (n=16). Treatment planning was based on CT/MRI scans (n=42) or on skull radiographs and anatomical landmarks (n=6). Computer-based treatment plans were used for most cases in which advanced imaging was available. Dogs were treated with parallel opposed beams (n=43), single dorsal beams (n=4), or three or more orthogonal beams (n=1). Blocks and wedges were used at the discretion of the radiation therapist but were not used in most cases. Ipsilateral mandibular lymph nodes were not irradiated in any dogs. The total radiation dose ranged from 16 to 40 Gy (median 24 Gy). Dose per fraction ranged from 4 to 10 Gy (median 8 Gy) [see Table]. Oral medications (including steroids, NSAIDs, and/or antibiotics) to help control clinical signs related to the nasal tumor or other conditions (e.g., osteoarthritis) were administered to 16 dogs during and/or after completion of PRT.

In 47 (98%) of the 48 dogs, the planned course of treatment was completed. The dog in which the course of therapy was not completed was euthanized after two of the three planned treatments, because the owner perceived a lack of response.

### Table

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>Dose Per Fraction (Gy)</th>
<th>Total Dose (Gy)</th>
<th>No. of Dogs</th>
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<tbody>
<tr>
<td>0-7-21</td>
<td>8</td>
<td>24</td>
<td>23</td>
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<tr>
<td>0-7-21</td>
<td>10</td>
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<tr>
<td>0-7-14</td>
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<td>7</td>
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<tr>
<td>0-7-14-21</td>
<td>5</td>
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<tr>
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<td>4</td>
<td>20</td>
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<tr>
<td>0-7</td>
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<td>16</td>
<td>1</td>
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In 39 (81%) dogs, at least one eye was irradiated. In 11 (28%) of these 39 dogs, ocular medications (including eye lubricants, topical cyclosporine, or antibiotic ointments) were prescribed during and/or after completion of PRT.

Because of the retrospective nature of this study, grading the adverse effects of RT using standardized schemes was not possible. Information on adverse effects during or after completion of PRT was available for 40 dogs, and acute adverse effects were reported in 14 (35%) dogs. Acute toxicities were generally mild and included (listed in order of decreasing frequency) oral mucositis, conjunctivitis, pitting edema in the irradiated field, dermatitis, and uveitis. Many dogs had multiple concurrent adverse effects. Asymptomatic alopecia, leukotrichia, and hyperpigmentation of the skin in the irradiated field were common in dogs that survived >3 months after PRT.

The incidence of acute ocular toxicity was difficult to discern, because some dogs were treated prophylactically with eye lubricants and topical ocular medications (e.g., antiinflammatory or antibiotic ointments/drops) during PRT and for 2 to 4 weeks after. Chronic ocular toxicities (i.e., conditions necessitating medications for >4 weeks after PRT) were reported in five (13%) of the 39 dogs that had at least one eye irradiated. Chronic toxicities included conjunctivitis, corneal ulceration or perforation, loss of vision, keratoconjunctivitis sicca, severe mucoid ocular discharge, cataract formation, blepharospasm, and uveitis. Most dogs that experienced chronic ocular toxicity had multiple concurrent ocular side effects.

One dog developed lymphadenomegaly, cytological evidence of mandibular lymph node metastasis, and recurrence of nasal signs 256 days after completion of the initial course of PRT. This dog was treated with a second course of PRT, in which both the nasal cavity and lymph node were irradiated.

Two dogs developed evidence of systemic metastasis after PRT. One of these had been treated for a stage T1 nasal adenocarcinoma and developed coughing and exercise intolerance 70 days after PRT. Thoracic radiographs revealed a multifocal nodular pattern consistent with metastasis, but this was not confirmed cytologically or histologically. The other dog, which had been treated for a stage T3 nasal adenocarcinoma, developed recurrence of nasal signs and cytological evidence of metastatic carcinoma to the liver, spleen, ribs, and scapulae 390 days after PRT.

Seizures were reported in four dogs 80 to 240 days (median 135 days) after PRT. Only one of these dogs had a history of seizure activity before PRT. Three of these dogs had been treated for stage T4 tumors (including brain invasion), and one had a stage T3 tumor. After the onset of seizures in one dog, a repeat CT scan confirmed progressive brain invasion by the tumor.

Response to PRT was evaluated in all dogs based on a retrospective review of medical records. In 32 (66%) of the 48 cases, clinical signs had completely resolved by the end of PRT or soon after. The remaining 16 dogs had only partial (n=12) or no (n=4) response to therapy. Dogs with partial or no response were combined in the data analysis.

No association was found between resolution of clinical signs and any of the analyzed risk factors. Thirty dogs experienced complete resolution of clinical signs but subsequently relapsed, while two remained free of clinical signs 113 and 883 days after PRT. Analysis of censored survival curves suggested a median response duration of 120 days (mean 209 days, range 20 to 1238 days [Figure 1]). One year after treatment, 10% of dogs were free of clinical signs; 2 years after treatment, 6% were free of clinical signs.

The only risk factor significantly associated with shorter response duration was the duration of signs before diagno-

![Figure 1](https://example.com/figure1.png)
signs resolved completely. The median survival time for dogs that did not have complete resolution of clinical signs (n=16) was 42 days, versus 255 days for dogs in which clinical signs resolved completely after treatment (n=32, \( P < 0.0001 \)) [Figure 4].

Eleven (23%) dogs that completely responded to the first course of PRT were treated with a second course of PRT when clinical signs recurred. The second course of PRT was initiated 70 to 573 days (median 171 days; mean 215 days) after the first course was completed. Dosing schedules were the same as the first course of PRT for 13 of 15 dogs. One of the remaining dogs received two additional 8-Gy doses at 6 and 22 months after the first treatment, and the other received two additional 8-Gy doses 1 week apart at an unknown interval after the first treatment. Nine (82%) of 11 dogs had a complete response to the second course of PRT. Duration of response varied, but it was >100 days in seven dogs.

**Discussion**

Definitive treatment for canine nasal tumors using external-beam RT consists of total radiation doses of 36 to 57 Gy divided into 10 to 19 fractions. Survival times after definitive RT range from 7 to 23 months, with 1-year survival rates of 37% to 60% and 2-year survival rates of 17% to 48%.\(^1\)\(^-\)\(^3\)\(^-\)\(^11\) Factors associated with longer survival include low stage,\(^1\)\(^,\)\(^3\)\(^-\)\(^9\)\(^-\)\(^11\) age <10 years,\(^1\)\(^1\) lack of metastasis to regional lymph nodes or lungs,\(^7\) lack of facial deformity, and complete resolution of clinical signs.\(^6\) In the present study, the overall median survival time was 146 days, with 25% of dogs alive at 1 year and 9% alive at 2 years after PRT. The shorter survival times for the dogs in the current study may be related to 1) more advanced-stage nasal disease than in previous studies; 2) a lower total radiation dose (i.e., median of 24 Gy in this study) compared to previous studies; 3) a fractionation schedule that could favor tumor repopulation (i.e., once-weekly treatments); and 4) a higher prevalence of dogs with concurrent illness compared to that reported in previous studies.

The shorter survival time in the authors’ study may have also been related to owner-specific factors. In this study, 60% of dogs were treated with PRT (instead of a definitive course of RT) at the owners’ request; many of these owners were specifically seeking therapies unlikely to result in adverse effects. Possibly, the owners of these dogs had less tolerance for the morbidity associated with treatment and/or lack of response to treatment, and they may have elected euthanasia sooner than owners of dogs in other studies.
The only factor significantly associated with survival time in this study was resolution of signs after PRT. The median survival time for dogs that did not have complete resolution of clinical signs was 42 days, versus 255 days for dogs that had complete resolution of signs after treatment. This finding is comparable to that of a 2001 study of dogs treated with orthovoltage RT, in which dogs with resolution of signs after RT had a median survival time of 476 days, versus 133 days for dogs with continued clinical signs.6

Few published studies of RT for canine nasal tumors address either the likelihood of response to treatment or the response duration, because at least some nasal signs persist long term in many dogs after treatment. Only one study addressed this issue objectively; in that study, 24 dogs were treated with Cobalt radiation for nasal carcinomas, and CT scans were performed at 1, 3, 6, and 12 months after treatment. The duration of local control was longer in the 11 dogs with marked tumor regression on CT (389 days) than in dogs without tumor regression (161 days).20 Other factors associated with longer response include surgical excision of the tumor before RT1 and low tumor stage.1,3

In the authors’ study, the complete response rate to PRT was 66%, with an overall response duration of 120 days. Response duration was assessed through careful examination of medical records and discussion with owners and referring veterinarians. However, it is possible that response rates were over- or underestimated because of the retrospective nature of the study.

The only factor significantly associated with longer response was “duration of clinical signs for ≥90 days before diagnosis.” It is likely that such tumors grew slowly, making them more responsive to PRT because of adequate oxygenation and a lack of tumor cell repopulation between fractions.21 Conversely, tumors resulting in a rapid onset of signs after RT had a median survival time of 476 days, versus 133 days for dogs with continued clinical signs.6

To date, only two other studies have evaluated treatment responses in dogs with nasal cancer after PRT or coarse radiation-fractionation schemes.2,4 In a retrospective study of 56 dogs with various histological types of sinonasal neoplasia, PRT was administered with a linear accelerator in four weekly 9-Gy fractions.2 Treatment plans and tumor stage determination were based solely on skull radiographs. Clinical signs improved by the end of PRT in 95% of these dogs, but most (89%) dogs were eventually euthanized as a result of their tumors. The median survival time from the last day of PRT was 212 days (range 38 to 386 days), with a 1-year survival rate of 45% and a 2-year survival rate of 15%2. There was no difference in survival between dogs that had carcinomas versus sarcomas or between stages of disease. In another report, 12 dogs with a variety of tumor types that were staged using skull radiographs were treated with PRT administered in four weekly, 9-Gy fractions.4 In these dogs, the median survival time was 441 days (range 301 to 1400 days), with 58% alive 1 year after PRT and 13% alive 2 years after PRT. No difference was seen in survival of dogs with different tumor types. In these reports (as in the present study), toxicities were mild, with most dogs responding to therapy. The longer median survival times and 1- and 2-year survival rates reported in these earlier studies may be because a larger portion of dogs had less advanced tumors than dogs in the present study. However, direct comparisons are difficult, because tumors in earlier studies were staged using skull radiographs rather than cross-sectional imaging.

The primary goal of PRT is to alleviate discomfort, not necessarily to prolong survival.22-24 Therefore, assessing outcomes after PRT is difficult, especially in veterinary patients. Patient response to PRT should ideally be measured both qualitatively and quantitatively. In people, response is assessed via questionnaires regarding mobility, pain, analgesic use, and overall improvement before, during, and after treatment.22-24 In one published study of PRT in dogs with various advanced-stage malignancies, 24 dogs were treated with 8-Gy fractions on days 0, 7, and 21—for a total dose of 24 Gy.16 Owners were asked to complete questionnaires that assessed the appetite, activity level, and lameness of their dog. Analgesic requirements, weight of the dog, and tumor response were also recorded before, during, and after therapy. Twenty (87%) of 23 dogs experienced partial or complete pain relief, and most owners felt that their pet had an improved quality of life and that they would consider the same treatment for another pet.16 Unfortunately, this type of information can rarely be obtained when reviewing records in a retrospective manner.

Prospective studies using detailed questionnaires addressing owner and clinician perceptions of patient status would improve the authors’ knowledge about responses to RT. Quantitative measurements of response should include measurement of the primary and metastatic tumor and evaluation of disease-free interval and survival time. Although the goal of PRT is not necessarily to prolong survival, improved quality of life may lead to longer survival. Many animals undergoing PRT might otherwise be euthanized because of the severity of their clinical signs. Hopefully, evaluation of both response duration and overall survival time gives a reasonable estimate for meaningful (i.e., good quality of life) survival. In the authors’ study, survival time was significantly affected only by response to therapy. Dogs that did not have a response to PRT were likely euthanized because of continued clinical signs and disease progression.

Palliative RT uses less intense dosing schedules and a lower total radiation dose than definitive RT, resulting in fewer acute adverse effects.16-18 In the present study, 35% of dogs had acute RT toxicity, which was generally mild and resolved with supportive care. This toxicity rate is lower than that reported for canine patients treated with definitive RT for nasal tumors, although differences in toxicity grading and follow-up make it somewhat difficult to compare results of this study to those of definitive RT studies.

Retrospective studies permit only limited assessment of toxicity. Ideally, prospective evaluations during treatment
could be documented using a published toxicity scheme. The reported occurrence of acute ocular, cutaneous, and oral adverse effects in dogs treated with definitive RT protocols is 67% to 95%, 92%, and 81% to 95%, respectively. Chronic ocular toxicity was seen in 13% of the dogs in the present study, which is lower than the 39% to 76% reported after definitive RT for nasal tumors but concern is still warranted given the increased morbidity and cost associated with ocular toxicity from PRT.

The ideal fractionation scheme for PRT has yet to be determined. Studies have not consistently revealed a dose-response relationship in people treated with coarse-fractionation schemes for metastatic bone cancer. Few veterinary studies have examined the effect of fractionation on outcome in palliative protocols, and in the present study no significant differences were seen in outcomes for dogs treated with different total doses or doses per fraction. Most published fractionation schemes for PRT in dogs are similar to those reported here and involve weekly treatments for 2 to 4 weeks using 8 to 10 Gy per treatment—for a total dose of 16 to 30 Gy. The advantages of a once-weekly treatment schedule include a decreased number of anesthetic episodes and decreased incidence of acute adverse effects (compared with daily therapy), because normal tissues have time to repair between treatments.

The disadvantages of a weekly protocol include the possibility of repopulation and repair of tumor cells and an increased chance of late-occurring adverse effects in susceptible tissues (e.g., muscle, nerve, and bone) as the dose per fraction is increased. Late adverse effects may include fibrosis and necrosis of tissues and (rarely) secondary tumor formation at the irradiated site. These effects are usually not seen until ≥1 year after radiation and are therefore uncommon in treated animals, which often do not survive this long after a course of PRT.

The occurrence of late side effects can be minimized by decreasing the fraction size. As an example, one of the treatment protocols in this study used five consecutive, daily 4-Gy fractions. Daily treatments allow little time for tumor cells to repair and repopulate, which may result in improved response. The lower dose per fraction (compared with most palliative protocols that use 8 to 10 Gy per fraction) decreases the chance of late side effects. In addition, the lower total dose (20 Gy) in this protocol may allow normal tissues to tolerate re-treatment if clinical signs recur. Clinicians might otherwise be hesitant to recommend re-treatment after protocols using higher total doses of radiation. Further studies to determine the ideal dosing scheme for PRT in dogs are indicated.

Eleven (23%) of the dogs in this study received a second course of PRT. All these dogs completely responded to the first course of PRT and were re-treated after relapse of clinical signs. Controlled studies on repeated irradiation are lacking in the veterinary literature. In one study, 51 dogs and cats with various tumors were given a second course of RT after an initial definitive course. A total of 86% had partial or complete response at 2 months after the second course of RT, and 41% were alive 1 year later. Complications after reirradiation have not been documented in the present study, although most dogs are deceased.

Clinicians and owners of dogs with nasal cancer may seek either alternatives to RT or synergistic therapies that may enhance quality of life and prolong survival compared with RT alone. Options include chemotherapy, pain medications, steroids, NSAIDs, and surgery. Chemotherapy has shown some potential for treatment of primary and metastatic sinonasal cancer, although large prospective studies have yet to be performed. Cyclooxygenase-2 (COX-2) inhibitors may alleviate pain and clinical signs, may have antineoplastic properties, and may act as radiation sensitizers. In a recent study of dogs with nasal cancer, survival times were longer for dogs treated with definitive RT followed by nasal cavity exenteration than for dogs treated with RT alone, although the surgical group had substantial postoperative morbidity. In addition to these adjunct therapies, improvements in RT treatment planning and delivery (such as 3D conformal RT and intensity-modulated RT) are increasingly available in veterinary medicine. The goals of these therapies are to improve dose distribution throughout the tumor volume and to decrease adverse effects in adjacent normal structures.

Conclusion

The goal of PRT is to improve the patient's quality of life while minimizing treatment-associated morbidity. In most dogs of this study, clinical signs resolved completely and usually with only mild signs of toxicity. The symptom-free intervals and overall survival times for nasal cancer cases treated with PRT are shorter than those in published results for definitive RT. Palliative RT should be considered as a treatment option in dogs with advanced local, metastatic, or severe concurrent disease that precludes definitive therapy. Hopefully the ongoing study of canine nasal cancer will result in decreased side effects, improved patient comfort, and prolonged survival.

Footnotes

- SPSS 10; Statistical Analytical Software, Chicago, IL

References


The histories of 67 cats diagnosed with chondrosarcoma (CSA) from 1987 to 2005 were reviewed. The mean age was 9.6 years, and males were 1.9 times more likely to be affected than females. Chondrosarcomas were diagnosed in the following sites: appendicular and axial skeleton, nasal cavity, facial bones, and extraskeletal sites. Of the 46 (70%) CSA associated with bone, 63% arose in long bones and 37% arose in flat bones. The remaining (30%) CSA arose in the subcutis. In cases available for follow-up (n=24), no definitive evidence of metastases was found. Cats that underwent radical surgical therapies were more likely to achieve long-term control or cure. J Am Anim Hosp Assoc 2008;44:124-130.

Introduction

Chondrosarcoma (CSA) is a malignant tumor in which the neoplastic cells produce chondroid and varying amounts of fibrillar matrix, but never osteoid.1 Feline CSA appears to grow slowly and invade locally, but it rarely metastasizes. Survival time seems to be lengthened by aggressive surgeries such as amputation, and information on therapies such as radiation is limited.2,3 The purposes of this study are to detail the signalment and tumor location in 67 cats diagnosed with CSA and to summarize the treatment methods for the 24 cats that were available for follow-up.

The characteristics and biological behavior of CSA in cats are not well defined. In one survey, only two of 256 neoplasms in cats were CSA.4 Feline CSA has been reported in studies of primary bone tumors, non-lymphoma tumors of the vertebral canal, and nasal tumors; also, several case reports have described CSA in cats, including two reports of CSA arising in multilobular chondromas.2,3,5-10 In one study of primary bone tumors in 24 cats, osteosarcoma (OSA) was the most common, followed by juxtacortical OSA and CSA.5 The CSAs reported in this study arose from the mandible, proximal tibia, and scapula. A subsequent study of primary bone tumors in cats indicates that CSA is as common as OSA, with tumors arising from the femur, ischium, metacarpal bones, and scapula.2

Chondrosarcomas also comprise a subset of sarcomas that arise in soft tissues. In a study of 23 cats with “soft-tissue sarcomas,” two cases were classified as CSA.11 In another study by Hendrick and Brooks, the histology and immunohistochemistry of sarcomas arising in vaccination sites were examined.12 Only one (2%) of the 46 postvaccinal sarcomas was a CSA; most of these sarcomas were fibrosarcomas and malignant fibrous histiocytomas. A similar incidence (2%) of CSA in vaccine-associated sarcomas was found in another immunohistochemical study.13

In contrast to CSA in cats, CSA in dogs is fairly well characterized. It accounts for approximately 10% of primary bone tumors in dogs and is, therefore, second only to OSA in incidence of primary bone tumors.14,15 In dogs, 61% of CSAs originate in flat bones; in one study, 50% of CSAs arose in the nasal cavity.16,17 Local recurrence, not metastasis, is the primary cause of treatment failure in dogs.16

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Materials and Methods

Surgical pathology reports dating between 1987 and 2005 were obtained for all cats diagnosed with CSA by the Laboratory of Pathology and Toxicology at the University of Pennsylvania School of Veterinary Medicine. Tissues were fixed in 10% buffered formalin, embedded in paraplast, cut, and stained with hematoxylin and eosin. Histopathology slides of all 67 cases were reviewed by one veterinary pathologist to confirm CSA. Chondrosarcomas are composed of interwoven bundles, sheets, and nests of cells within a lightly basophilic, chondroid matrix. Cells have a moderate amount of amphophilic cytoplasm, indistinct borders, and large ovoid nuclei. Cellular and nuclear pleomorphism, binucleation, and frequent mitoses are common features. Tumor cells may produce neoplastic chondroid, fibrillar matrix, and bone formed by endochondral ossification of tumor cartilage [see Figure]. Cats with tumors producing varying amounts of both tumor chondroid and tumor osteoid were excluded from the study.

Information about age, sex, breed, and tumor location was obtained from the biopsy reports. Tumors were classified as arising from the nasal cavity, appendicular skeleton (i.e., humerus, radius/ulna, carpus, femur, tibia, tarsus, digit), axial skeleton (i.e., scapula, sternum, rib, vertebra, pelvis), facial bones (i.e., skull, maxilla, mandible), and extraskeletal regions (i.e., subcutaneous tissues, subcutis). Bone tumors were also categorized as those involving bones that develop via endochondral ossification (long bones) or those involving bones that develop from intramembranous ossification (flat bones). Tumors within the subcutis were further categorized as originating from the axilla, interscapular region, thoracic region, flank, hind limb, or lumbar area.

Additional information was obtained for all cases from the form submitted by the referring veterinarian that accompanies every biopsy sample. Information obtained from this form included species, breed, sex, birth date, case history, gross appearance of the tumor, number of lesions, size, duration and rate of growth, treatment, and location. A section of the form was available to indicate the type of sample submitted (e.g., wedge, entire specimen, Tru-Cut, punch, fragment, endoscopic, or other), and yes/no questions were provided to indicate lymph node involvement, tumor encapsulation, and excisional biopsy. Follow-up information was obtained from hospital records and questionnaires that were sent to the referring veterinarians. Additional clinical data (i.e., current status, survival time, etc.) was noted.

Figure—Neoplastic cells are arranged in nests and sheets and surrounded by lightly basophilic, chondroid matrix. Note marked nuclear and cellular pleomorphism and binucleate cells. Neoplastic cells have moderate amounts of finely vacuolated, amphophilic cytoplasm; large, oval, finely stippled nuclei; and prominent nucleoli. Mitoses are often variable. (Hematoxylin and eosin stain, A 10×; B 20×; C 40×.)
radiographs, blood work, clinical signs, and treatment) were available for 24 cats. For the purposes of this study, treatment options included incisional and excisional biopsies, radical surgery (e.g., amputation), or chemotherapy and/or radiation therapy. Notation was made if the tumor was located in a previous vaccination site.

To assess differences in age, breed, and sex, cats with CSA were compared to the general population of cats with surgical accessions during the same time period. Categorical data were compared using either the chi-square or Fisher’s exact test, and Student’s \( t \)-test was used for continuous data. Analysis of variance was used to examine tumor location with regard to age. The chi-square test was used to examine tumor location with regard to sex. The Kaplan-Meier product limit method was used to determine the median survival time for cats with CSA. When applicable, data are presented as odds ratios (ORs) with 95% confidence limits (CIs). All analyses were performed using SAS statistical software. A \( P \) value <0.05 was considered statistically significant.

Results

Age Distribution

The mean age of affected cats \( n=67 \) was 9.6 years, and the median age was 9 years (range 2 to 18 years). No significant difference was found in mean age with respect to the general population of cats seen in the surgical pathology service during the same time period (9.6 years versus 8.8 years; \( P=0.09 \)); also, no significant difference was found in age with respect to tumor location.

Breed

Most \( n=57; 85\% \) of the cats were domestic shorthairs, followed by domestic longhairs \( n=5; 7.5\% \), unspecified rare breeds \( n=2; 3\% \), Siamese \( n=2; 3\% \), and Persian \( n=1; 1.5\% \). When compared to the general population of cats submitted to the surgical pathology service, no breed predilection was noted.

Sex Distribution

Of the 67 affected cats, 42 \( 63\% \) were males and 25 \( 37\% \) were females. When compared to the surgical pathology population, males were more frequently affected than females (OR 1.9; 95% CIs 1.1, 3.1; \( P=0.014 \)). No statistically significant difference was seen between males and females with respect to tumor location.

Tumor Morphology/Histology

Tumor location was reported in 66 of the 67 cases. Of the 41 cases in which encapsulation was noted on the submission form, 26 \( 63\% \) of the tumors were encapsulated, and 15 \( 37\% \) were not. Involvement of regional lymph nodes, based on physical examination, was reported in 58 cases. Of these 58 cases, 56 \( 97\% \) had no lymph node involvement, and two \( 3\% \) had possible involvement, although this was not confirmed via biopsy in either case. Follow-up data were available for one cat, which is still alive with no recurrence or metastatic disease. The tumors were generally described (by the referring veterinarians) as white-tan, often cavitated, glistening, and firm. Histologically, these tumors were composed of bundles, nests, and sheets of neoplastic chondrocytes; some contained areas of necrosis, endochondral ossification, or mineralization. Aggressive histological features included severe pleomorphism, bi- or trinucleation, and numerous mitotic figures (approximately two to four per high-power field).

Tumor Location

Forty-six \( 70\% \) of the tumors were associated with bone. Thirteen \( 28\% \) tumors arose from the axial skeleton and included the following sites: scapula \( 15\% \), vertebra \( 6.5\% \), pelvis \( 2.2\% \), and sternum \( 4.3\% \). Appendicular CSAs accounted for 52 \( n=24 \); and sites included the humerus \( 6.5\% \), radius/ulna \( 4.3\% \), femur \( 13\% \), tibia \( 8.7\% \), carpus \( 4.3\% \), tarsus \( 2.2\% \), and digits \( 13\% \). Six \( 13\% \) CSAs arose from facial bones, including the skull bones \( 4.3\% \) and mandibular/maxillary bones \( 8.7\% \). Three \( 6.5\% \) CSAs arose from the nasal cavity [Table 1].

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chondrosarcoma (CSA) Location in the Axial and Appendicular Skeleton</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>Bone-only CSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial Skeleton</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scapula</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Vertebrae</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Sternum</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Appendicular Skeleton</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>Radius/ulna</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Femur</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Tibia</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Carpus</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Tarsus</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Digits</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td><strong>Facial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Mandible/maxilla</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Nasal</td>
<td>3</td>
<td>6.5</td>
</tr>
</tbody>
</table>
The locations of tumors were further subdivided into those from bones that develop via endochondral ossification (i.e., vertebra, sternum, ribs, humerus, radius, ulna, femur, tibia, carpus, tarsus, and digits) and those from bones that undergo intramembranous ossification (i.e., facial bones, nasal turbinates, scapula, and pelvis). Of the CSAs that involved bones, 63% involved bones arising from endochondral ossification, and 37% involved bones arising from intramembranous ossification [Table 2].

Twenty (30%) cases of CSA involved subcutaneous sites and were categorized based on the following locations: axilla (5%), interscapular region (15%), thoracic region (10%), flank (15%), lumbar area (5%), hind limb (45%), and unspecified subcutaneous locale (5%). Histopathology reports regarding several of the subcutaneous tumors indicated debate as to whether these tumors represented vaccine-site sarcomas. In one report, the presence of grey-blue material within macrophages, which is consistent with vaccine product, was noted. The overall site distributions of CSAs were 44% in long bones, 26% in flat bones, and 30% in the subcutis [Table 2].

Follow-up Information

Information about the current status of the cat was available for 24 cases from 1998 to 2005. The remainder of the medical records had been discarded. Eleven (45.8%) cats are still alive with no recurrence or metastases. Most of these 11 cats had radical surgeries performed, including amputation, hemipelvectomy, and mandibulectomy. Only one of these 11 cats had an excisional biopsy only, in which the margins were clean; this particular tumor arose from the subcutis. The durations of follow-up for these 11 cats ranged from 0 to 2118 days (mean 490 days).

Four (16.7%) cats are currently alive but have progression of the primary tumor. All four of these cats had incisional biopsies only. One of these cats with local recurrence had a limb amputation performed 108 days later; this cat is still alive with no recurrence after the amputation, and it is included in the two survival categories. The durations of follow-up for these four cats ranged from 31 to 302 days (mean 167 days). (The cat that underwent amputation was excluded.)

Nine (37.5%) cats were euthanized for reasons related to the CSA, including decreased quality of life and poor prognosis. Five of these euthanized cats had incisional biopsies; one had a laminectomy, one had chemotherapy and radiation in addition to the excisional biopsy, and two had amputations (both of which had “dirty” surgical margins) [Table 3]. The survival times from date of diagnosis of euthanized cats ranged from 0 to 315 days (mean 85 days). The five euthanized cats that only had incisional biopsies survived 0 to 40 days. The cat that had the laminectomy was euthanized the day after surgery; the two that underwent amputations survived 137 and 237 days; and the cat that had an excisional biopsy and adjuvant therapy survived 315 days.

In summary, in the nine cats that received incisional biopsies only (i.e., effectively no treatment), four had progression of the tumor, and five were euthanized for reasons related to CSA. Fifteen cats received surgical treatment. Of the 12 cats that had radical surgery performed, 10 (83%) are still alive, and two (17%) were euthanized (the two euthanized cats had “dirty” surgical margins). Three treated cats had excisional biopsies performed; one with clean margins is still alive, and the two with “dirty” margins were

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>Bone-only CSA (%)</th>
<th>All CSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Bone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebra</td>
<td>3</td>
<td>6.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Sternum/ribs</td>
<td>2</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>Humerus</td>
<td>3</td>
<td>6.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Radius/ulna</td>
<td>2</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Femur</td>
<td>6</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Tibia</td>
<td>4</td>
<td>8.7</td>
<td>6</td>
</tr>
<tr>
<td>Carpus</td>
<td>2</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>Tarsus</td>
<td>1</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Digit</td>
<td>6</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Flat Bone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>2</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>Mandible/ maxilla</td>
<td>4</td>
<td>8.7</td>
<td>6</td>
</tr>
<tr>
<td>Nasal</td>
<td>3</td>
<td>6.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Scapula</td>
<td>7</td>
<td>15</td>
<td>10.6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Subcutis</td>
<td>20</td>
<td>N/A*</td>
<td>30</td>
</tr>
<tr>
<td>Axilla</td>
<td>1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Interscapular</td>
<td>3</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Flank</td>
<td>3</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Hind limb</td>
<td>9</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Unspecified subcutaneous</td>
<td>1</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

*N/A = not applicable

---

**Table 2**

Chondrosarcoma (CSA) Overall Site Distribution
euthanized. Median survival time could not be calculated, because 50% of the cats are alive, and the overall occurrence rate for this particular tumor is low.

Thoracic radiographs were available for 16 of the 24 follow-up cases. Almost all thoracic radiographs were taken at the time of diagnosis; radiographs were taken in one cat every 2 months, with no signs of metastatic disease. Possible lung metastases were reported in only three (18.7%) cats—two of which are still alive with no recurrence of the tumor. These cats were rechecked by the veterinarian at 563 and 918 days after radiographs were available, and no abnormalities were noted. The third cat

<table>
<thead>
<tr>
<th>Status and Follow-up Duration</th>
<th>n (% of CSA)</th>
<th>Tumor Site</th>
<th>Therapeutic Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive with no recurrence or metastases</td>
<td>11 (45.8)</td>
<td>Digit</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutis (hind limb)</td>
<td>Hemipelvectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Humerus</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digit</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mandible</td>
<td>Partial mandibulectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scapula</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutis (interscapular)</td>
<td>Excision; margins clean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Femur</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tibia</td>
<td>Amputation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Subcutis (hind limb)</td>
<td>Amputation</td>
</tr>
<tr>
<td>Alive with progression of tumor</td>
<td>4 (16.7)</td>
<td>Scapula</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carpus</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radius/ulna</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Subcutis (hind limb)</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td>Euthanized</td>
<td>9 (37.5)</td>
<td>Subcutis (hind limb)</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maxilla</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Femur</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maxilla</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal</td>
<td>Incisional biopsy</td>
</tr>
<tr>
<td>Survival time: 1 d</td>
<td>Vertebra</td>
<td>Laminectomy/biopsy</td>
<td></td>
</tr>
<tr>
<td>Survival time: 137-237 d</td>
<td>Scapula</td>
<td>Amputation; incisional biopsy after recurrence at surgical site</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tarsus</td>
<td>Amputation; margins “dirty”</td>
</tr>
<tr>
<td>Survival time: 315 d</td>
<td>Subcutis; flank</td>
<td>Excision, chemotherapy (Adriamycin, Cytoxan), radiation</td>
<td></td>
</tr>
</tbody>
</table>

* Same cat: tumor progressed after initial incisional biopsy; 108 days later, the limb was amputated with no further recurrence.
with possible lung metastases is still alive with local progression of tumor; a recheck evaluation 31 days later found no clinical signs associated with pulmonary disease. Radiographs of the tumor were taken in 19 cases; the most commonly reported findings included soft-tissue swelling and bone lysis.

Results of blood work, reported in 18 of the 24 cases, were normal in all but three cats. One of these three cats that had been treated with chemotherapy was leukopenic, and two of these cats had mildly elevated amylase.

In three of the 24 cats available for follow-up, the veterinarians reported that the locations corresponded to vaccination sites.

**Discussion**

Although CSA is one of the more common bone tumors in cats, its overall incidence is relatively low. To date, published reports on its clinical characteristics and prognosis have been few. Much of the literature on CSA in cats consists of single case reports. In the present study, the signalment, tumor locations, and, when available, treatment protocols and outcomes were examined.

The mean age (9.6 years) of all cats with CSA in this study was slightly older than that in previous reports of CSA in cats. The finding that most affected cats were domestic shorthairs (85%) is consistent with the normal breed distribution in the feline population. A significant difference was seen regarding sex distribution; males were 1.9 times more likely to develop CSA than females. This finding is in contrast to the sex distribution in dogs with CSA, in which females are affected 1.5 times more frequently than males.

Although CSAs have been reported in both long bones and flat bones, the published data are inadequate to determine site predilection in cats. In this study, most (46 of 67) CSAs were associated with bone; 63% involved long bones, and 37% involved flat bones. These findings are again in sharp contrast to site predilection in dogs, in which 61% of CSAs arise in flat bones. Of the long-bone CSAs in cats, the femur and digits were the most common sites (13% each), followed by the tibia (8.7%). The scapula was the most commonly affected flat bone as well as the most commonly affected of all bones (15%).

Feline CSAs do arise in vaccination sites, although fibrosarcomas are more widely reported. Thirty percent of CSAs in cats involved the soft tissues, with locations reflecting vaccination sites, including interscapular, lateral thorax/axilla, flank, lumbar, and hind limb. In this study, the hind-limb subcuticular region was the most commonly affected site. Interestingly, the hind-limb region is often the vaccination site reserved for rabies vaccine (right rear) and feline leukemia virus (left rear) in accordance with the Vaccine-Associated Feline Sarcoma Task Force guidelines set forth in 1996. In this study, vaccine product was seen in one of these tumors, and most of the subcuticular CSAs were suspected to be injection-related sarcomas based on their location and often aggressive histological features.

Because only a limited number of cases were available for follow-up, it is difficult to ascertain whether subcutaneous CSAs are more clinically aggressive than primary bone CSAs. In fact, in the cases available, survival appeared to depend more on the type and success of therapeutic intervention. Of the 24 cats for which follow-up information was available, 45.8% were still alive with no recurrence of the primary tumor or metastases. It is important to note that follow-up evaluation for evidence of metastasis was limited. Most of the cats that were still alive with no recurrence or metastases had undergone radical surgeries, including amputation, hemipelvectomy, and mandibulectomy; only one of these cats had an excisional biopsy performed, and the margins were clean. All four of the cats with local progression of the primary tumor had only incisional biopsies performed. Five of the nine euthanized cats had only incisional biopsies as well. One cat had an incisional biopsy and adjuvant therapy, including radiation and chemotherapy. Two of the nine euthanized cats had amputations, and one had a laminectomy; in all cases, the surgical margins were “dirty.” Moreover, the survival time from diagnosis in euthanized cats that had only an incisional biopsy was 0 to 40 days. This may reflect an unwillingness on the part of the owner to elect more radical surgery and instead opting for euthanasia. Interestingly, the survival times of the two cats with amputations increased to 137 and 237 days; the cat that received adjuvant therapy lived 315 days.

Of the three cats with reported lung masses (two of which were followed for 1.5 to 2.5 years), none showed any clinical signs of pulmonary disease, and no lung biopsies were performed. No cats in this study were euthanized because of lung metastasis or metastatic disease; this is in contrast to the situation in dogs, in which 20.5% of deaths (either from the disease or euthanasia) are caused by lung metastases.

**Conclusion**

The overall incidence of CSA in the feline population is low, and the cases available were subject to the difficulties inherent in retrospective studies and the retrieval of records from multiple veterinary clinics. In spite of these limitations, some conclusions as to treatment and prognosis can be drawn from the available data. In summary, CSA in cats tends to be locally invasive but not prone to metastasize. Cats in this study that underwent aggressive surgery had a higher likelihood of achieving full recoveries.

**Footnotes**

* Version 9.1; SAS Institute, Cary, NC 27513

**Acknowledgments**

The authors thank Dr. Frances Shofer for providing the statistical analyses for this paper.

**References**

Utility of Serum Cystatin C as a Clinical Measure of Renal Function in Dogs

A human kit for cystatin C determination was evaluated for use with canine sera. A reference range was also established. The association between cystatin C and glomerular filtration rate (GFR) was evaluated in 60 dogs with various diseases, by using exogenous creatinine plasma clearance (ECPC) as a measure of GFR. The correlation between cystatin C and ECPC (correlation coefficient \( r = -0.630; P<0.001 \)) was stronger than the correlation between serum creatinine and ECPC \( (r = -0.572; P<0.001) \). Nonrenal diseases (e.g., neoplasia, infection) did not influence serum cystatin C concentration. Test sensitivity was significantly better \( (P<0.001) \) for cystatin C (76%) than for creatinine (65%). Specificities for the two tests were 87% and 91%, respectively. J Am Anim Hosp Assoc 2008;44:131-138.

**Introduction**

Glomerular filtration rate (GFR) is widely accepted as the most accurate measure of renal excretory function. Renal clearance is defined as the volume of plasma that has been cleared of a particular substance per unit of time, with GFR estimated by renal clearance of an appropriate filtration marker. The changing concentration of this marker can be measured in plasma and urine or in plasma alone. However, available methods for estimating GFR are impractical for widespread clinical use. Therefore, serum creatinine concentration is most often used to assess renal excretory function. This test is reasonably specific but somewhat insensitive for detecting reduced GFR. Creatinine originates from the skeletal muscle and, to a lesser extent, food, so blood levels are influenced by muscle mass and (to a lesser extent) food intake.

Cystatin C is a protease inhibitor that belongs to the family of cystatines. Together with the stefines and kinogenes, the cystatines form the super-family of cysteine proteinase inhibitors. The cystatin C molecule consists of a single polypeptide chain having 120 amino acids and a molecular weight of 13,359 kilodalton (kDa). The molecule is not glycosylated, and it has an isoelectric point of 9.3. Cystatin C is produced by all nucleated cells within the body and is released during phagocytosis and inflammation.

The major function of cystatin C is to control inflammation by inhibiting lysosomal proteases. Cystatin C helps to regulate intracellular and extracellular protein/peptide catabolism, as well as the penetration of cancer cells into tissues. Recent studies have also demonstrated antimicrobial properties associated with this protein. The rate of cystatin C synthesis is constant (housekeeping type), independent of age and gender, and unaltered by inflammatory processes or neoplasia. High concentrations can be found in serum, seminal fluid, cerebrospinal fluid (CSF), and synovial fluid.

Cystatin C fulfills many criteria of an ideal GFR marker, because it is filtered by the glomeruli without any tubular secretion. The molecule passes through the glomeruli easily because of its low molecular weight.
and positive charge at physiological pH. Cystatin C is catabolized completely within the proximal tubular cells, so urine concentration is typically low\textsuperscript{13,15} and unaltered by diseases of the proximal tubules.\textsuperscript{16} Cystatin C is eliminated exclusively by the kidneys\textsuperscript{17} and is superior to serum creatinine as a marker of GFR in people.\textsuperscript{13,18-21} However, few published studies explore the diagnostic utility of cystatin C in dogs.\textsuperscript{22,23}

The main goals of the present study were to validate a human cystatin C test kit in dogs and to establish a canine reference range. A third goal was to compare serum cystatin C concentrations with exogenous creatinine plasma clearance (ECPC) to assess its use as a measure of renal function.

**Materials and Methods**

**Validation of the Test Kit**

The test kit was validated using a particle-enhanced turbidimetric (PET) assay\textsuperscript{a} designed to quantify cystatin C levels in human serum or plasma. In this technique, cystatin C binds to rabbit antihuman cystatin C antibody that has been coupled to polystyrene particles. The resulting change in turbidity is proportional to the cystatin C concentration in the sample. The assay was set up on an automatic analyzer\textsuperscript{b} according to the manufacturer’s instructions.

Two serum pools were created to evaluate measures of assay quality. One pool consisted of sera from eight dogs with increased serum creatinine concentrations, and the other consisted of sera from eight dogs with normal values. Interassay variability was assessed by freezing 11 serum samples (-80°C) from each of the two serum pools and then testing one daily for 10 consecutive days, with the 11th sample thawed and tested after 365 days. Dilutional parallelism was determined by serial dilution with physiological saline, so as to produce concentrations that were 75%, 50%, and 25% of the original. Determining cystatin C recovery was not possible, because a purified source of canine cystatin C was not available, and the authors’ research facilities were not equipped to purify it.

To evaluate intraindividual variation, blood samples were obtained at 0, 360, and 720 minutes from 27 dogs with various degrees of kidney function. All dogs had been fasted for 12 hours.

**Establishment of Reference Ranges**

Blood samples were taken from 99 dogs presented for annual checkup examinations. All dogs had been fasted for 12 hours and had normal physical examinations, complete blood counts, biochemical profiles, and urinalyses (i.e., stick, specific gravity, sediment). Blood and urine were collected by jugular vein puncture and cystocenteses, respectively. Serum samples for cystatin C measurement were frozen (-80°C) until analyzed.

Owners gave informed consent before any blood and urine samples were obtained from dogs, in accordance with published laws and university policy.

**Comparison of Cystatin C and ECPC in Dogs**

Ideally, GFR should be assessed with a urinary inulin clearance, which is considered the gold standard. However, urinary clearance testing was considered impractical in a hospital facility, so GFR was assessed by ECPC, which is a crude but accepted substitute.\textsuperscript{24}

Exogenous creatinine plasma clearance was performed in 60 dogs that had been diagnosed with various renal and nonrenal diseases. Of these dogs, 27 were suspected of having chronic kidney disease, with the remaining 33 being assessed for renal function before treatment with potentially nephrotoxic substances. Final diagnoses were based on histopathology/cytology (n=24), serology (n=11), ECPC (n=17), and other methods (e.g., endocrine testing, abdominal ultrasonography, and echocardiography). Dogs had been fasted for 12 hours before examination. All were clinically well hydrated.

A standardized procedure was used to assess all 60 dogs. First, serum creatinine concentration was determined, followed by intravenous injection with a 5% creatinine solution\textsuperscript{d} dosed at 60 to 125 mg/kg. The exact dosage depended on body mass, with lower concentrations applied to larger dogs. Twelve to 15 blood samples were obtained over the next 10 hours, so that serum creatinine concentrations could be measured enzymatically.\textsuperscript{b} The upper limit of the in-house reference range for serum creatinine was 106 µmol/L (1.2 mg/dL). The area under the curve (AUC) was calculated with a trapezoidal approach (i.e., noncompartmental model).\textsuperscript{1}

The ECPC was calculated as 100 multiplied by the amount of injected creatinine divided by the AUC (100 x injected creatinine/AUC).\textsuperscript{24-26} An ECPC ≥3 mL/kg per minute was considered normal. Values of 2.00 to 2.99 mL/kg per minute were considered to be slightly reduced, and values ≤1.99 mL/kg per minute were considered to be markedly reduced. These values were compared with the reference range for cystatin C that was already established (see above).

**Statistics**

Statistical analyses were performed using version 13.0 of SPSS.\textsuperscript{d} Descriptive statistics were computed for the cystatin C test kit validation and reference range calculations. Kolmogorov-Smirnov analysis was used to determine if the age and gender variables used in the reference range calculations were normally distributed and if the reference range itself was normally distributed. Pearson’s correlation statistics were used to assess the association between cystatin C and age, weight, or gender. Correlational analysis was also used to assess the relationships between ECPC and serum creatinine, between ECPC and cystatin C, and between serum cystatin C and presence of nonrenal disease. Receiver operating characteristics (ROC) analysis was used to compare sensitivity, specificity, and positive/negative predictive values for both serum cystatin C and serum creatinine. Sensitivity is defined as true positives divided by the sum of true positives and false negatives, and...
specificity is defined as true negatives divided by the sum of false positives and true negatives. Positive predictive value is defined as true positives divided by the sum of true positives and false positives, and negative predictive value is defined as true negatives divided by the sum of true negatives and false negatives. Statistical significance was defined as $P<0.05$.

**Results**

**Validation of the Test Kit**
The intraassay coefficients of variation were 1.76% for the serum pool consisting of the eight dogs with high creatinine values, and 3.85% for the serum pool consisting of the eight dogs with normal values. The interassay coefficients of variation for these two groups were 2.95% and 3.64%, respectively [see Table]. Values for the two serum pools were 8% and 11% higher (respectively) after 365 days. An almost linear decrease in cystatin C concentration was observed after serial dilution (75%, 50%, 25%). The correlation coefficient ($r$) was 0.992 ($P<0.01$) for those with high creatinine, and $r$ was 0.989 ($P<0.05$) for those with normal creatinine [Figures 1A, 1B].

**Intraindividual Variations**
Serum cystatin C concentrations remained stable over time in the 27 dogs sampled at 0, 360, and 720 minutes ($r=0.964$, 0.954, respectively; $P<0.001$).

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**Figures 1A, 1B**—Correlation between the observed and calculated cystatin C concentrations of different dilutions of pooled canine sera (1A=pool with higher concentrations, n=8; 1B=pool with normal concentrations, n=8).

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**Table**

<table>
<thead>
<tr>
<th>Cystatin C Concentrations</th>
<th>Intraassay Variability</th>
<th>Interassay Variability</th>
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<tr>
<td><strong>Pooled Sera Used</strong></td>
<td>High Creatinine</td>
<td>Normal Creatinine</td>
</tr>
<tr>
<td>Mean (mg/L)</td>
<td>2.177</td>
<td>1.607</td>
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<tr>
<td>Standard deviation</td>
<td>0.038</td>
<td>0.061</td>
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<tr>
<td>Coefficient of variation (%)</td>
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<td>Number of replicates</td>
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* PET=particle-enhanced turbidimetric
† One pool was from dogs (n=8) with high serum creatinine concentrations, and another was from dogs (n=8) with normal serum creatinine concentrations.
Establishment of Reference Values
The 99 reference dogs ranged in age from 3 months to 13 years (median 4 years). Twenty-five dogs were intact females, 27 were spayed females, 26 were intact males, and 21 were neutered males. Body weight ranged from 5 to 42 kg (median 25 kg). Kolmogorov-Smirnov analysis suggested that age and weight were normally distributed. Breeds represented by more than one case in the reference group were German shepherd dog (n=18); golden retriever (n=8); Labrador retriever (n=6); dachshund (n=4); Magyar vizsla, border collie, Belgian Tervuren, Dalmatian, Siberian husky (n=3 each); and Bernese mountain dog, Irish wolfhound, Schapendoes, boxer, and rottweiler (n=2 each). The remaining 38 cases consisted of other breeds (n=12) or mixed breeds (n=26).

Serum cystatin C concentrations ranged from 0.49 to 1.81 mg/L (mean 1.144, standard deviation [SD] ± 0.231). The 0.025 and 0.975 quantiles (determined as mean ± 2 SD) were 0.682 mg/L and 1.606 mg/L, respectively, suggesting a reference range of 0.68 to 1.6 mg/L. Kolmogorov-Smirnov analysis suggested that cystatin C values were normally distributed.

Serum creatinine concentrations for the 99 dogs ranged from 56 to 103 µmol/L (0.63 to 1.17 mg/dL), with a mean ± SD of 81.90±13.29 µmol/L. A serum creatinine reference range for these 99 dogs would be 55.31 to 108.5 µmol/L (0.63 to 1.23 mg/dL), based on 0.025 and 0.975 quantiles. This almost matched the established in-house reference range, so the upper limit for serum creatinine was left as the in-house value of 106 µmol/L (1.2 mg/dL).

Influence of Age, Weight, and Gender
No significant correlation was found between serum cystatin C and age (r=0.022; P>0.05) or between cystatin C and weight (r=0.036; P>0.05). Serum cystatin C concentrations were similar in the 52 female (mean ± SD 1.13±0.24 mg/L) and 47 male (mean ± SD 1.15±0.21 mg/L) dogs [Figure 2].

Comparison of Cystatin C and ECPC in Dogs
The ages for these 60 dogs ranged from 0.5 to 15 years (median 5 years), and the weights ranged from 7 to 51.8 kg (median 27.2 kg). Twenty-five females (16 spayed) and 35 males (eight neutered) were represented. Breeds that were represented by more than one case were Bernese mountain dog (n=6), boxer (n=4), beagle (n=3), German shepherd dog (n=3), and West Highland white terrier (n=2). The remainder consisted of other purebred (n=15) or mixed-breed (n=27) dogs. These dogs were ultimately diagnosed with neoplasia (n=7), chronic kidney disease (n=24), neoplasia and concurrent chronic kidney disease (n=15), infection (n=10), or four other diseases (two endocrinopathies, one psychogenic drinker, and one mitral insufficiency).

Serum creatinine values for these 60 dogs ranged from 42 to 590 µmol/L (0.46 to 6.67 mg/dL), with a median of 91 µmol/L. Forty-three percent of these values were above the reference range (i.e., >106 µmol/L [>1.2 mg/dL]). Cystatin C values ranged from 0.79 to 5.97 mg/L (median 1.65 mg/L), with 52% having elevated concentrations (>1.6 mg/L). Results of ECPC ranged from 0.3 to 5.0 mL/kg per minute (median 2.6 mL/kg per minute), with 38% (23 of 60) dogs having normal (≥3 mL/kg per minute) values, and 62% (37 of 60) having abnormal values. The abnormal ECPC values consisted of slightly decreased ECPC (i.e., 2.00 to 2.99 mL/kg per minute) in 22 dogs and markedly decreased ECPC (≤1.99 mL/kg per minute) in 15 dogs.

Correlation Among ECPC, Creatinine, and Cystatin C
A significant inverse correlation was seen between ECPC and serum creatinine in these 60 dogs (r=-0.572; P<0.001), which appeared less than linear [Figure 3A]. Also, a significant and less than linear inverse correlation (r=-0.630; P<0.001) was seen between ECPC and serum cystatin C, but the relationship appeared more linear than the one between ECPC and creatinine [Figure 3B]. A strong and significant positive correlation (r=0.886; P<0.001) was seen between serum creatinine and serum cystatin C, which approached linearity [Figure 4].

Correlation Between Creatinine or Cystatin C and the Degree of Renal Function
Dogs were assigned to three groups according to the results of the ECPC. Group 1 had normal ECPC (≥3 mL/kg per minute; n=23); group 2 had slightly reduced ECPC (2.00 to 2.99 mL/kg per minute; n=22); and group 3 had markedly reduced ECPC (≤1.99 mL/kg per minute; n=15). Serum creatinine and cystatin C concentrations were compared within these groups [Figures 5A, 5B]. The median serum concentration of cystatin C in dogs with slightly reduced ECPC (Group 2) was outside the reference range, while the median serum creatinine concentration was within the reference range. All dogs with markedly reduced ECPC
(Group 3) had elevated serum cystatin C concentrations, but some had normal serum creatinine values.

Comparison of Cystatin C Among Final Diagnoses
Dogs were assigned to five groups according to their final diagnosis. Cystatin C concentrations in the different groups were compared to explore the influence of nonrenal diseases on cystatin C. Almost all dogs with nonrenal diseases and normal GFR had cystatin C values within the reference range [Figure 6], and all such dogs had normal creatinine values.

Sensitivity, Specificity, ROC Analysis, Positive and Negative Predictive Values
The sensitivity for detecting decreased ECPC (<3.0 mL/kg per minute) was 76% for cystatin C, but sensitivity was only 65% for serum creatinine (P<0.001). Specificities were similar between serum cystatin C (87%) and serum creatinine (91%). The ROC analysis suggests that cystatin C is significantly better (P<0.001) than serum creatinine at identifying reduced ECPC [Figure 7]. The positive and negative predictive values for detecting decreased ECPC were 90% and 69% (respectively) for serum cystatin C, and they were 92% and 62% (respectively) for serum creatinine.

Discussion
Identification of renal disease is important in canine medicine, but early diagnosis remains difficult in some cases. Serum creatinine concentration rises as GFR falls, but azotemia is not usually clinically apparent in dogs until GFR decreases by ≥75%. Therefore, creatinine screening tests may not detect mildly decreased renal function. Mild kidney disease in dogs can be reliably diagnosed only by performing time-consuming clearance procedures, such as ECPC or iohexol plasma clearance. In contrast, human studies have focused on endogenous, low-molecular-weight proteins as a way to detect early renal dysfunction.18 Multiple studies of GFR reduction in people have shown that serum cystatin C concentration has better sensitivity and negative predictive value than serum creatinine.16,27-30 The authors’ study suggests that the human PET assay is valid for measuring cystatin C in dogs. This test is rapid, precise, and inexpensive. It measures cystatin C in a linear and proportional manner, which is consistent with results of other veterinary studies.22,23 Unfortunately, the authors were unable to determine percent recovery at their facility. This is a limitation of this study, in that the authors were not
able to definitively prove that the PET assay was measuring cystatin C.

The exact genetic structure of canine cystatin C is unknown, but a high degree of homology appears to exist between people, cattle, mice, and rats. One genetic sequence (i.e., the so-called μ-trace) has a high degree of homology between people and dogs.31-35 The authors hypothesized that the PET assay might reliably detect canine cystatin C, given this homology between people and dogs and the high degree of correlation between the PET assay and renal function.

This study demonstrated that serum cystatin C is stable over time and can be reliably measured after being frozen at -80°C for 1 year. The same has been shown in people.36 High concentrations of proteinase inhibitors (e.g., α2-macroglobulin, α1-protease inhibitor, and kinogenes) and natural preservatives, such as transferrin, add stability to the blood.18

The reference range for cystatin C in this study was 0.68 to 1.6 mg/L, which is slightly above the range observed in other veterinary and human studies.22,23,37-39 This slight difference
may have been caused by slight variations in the assay principle or reagents or by differences in instrumentation.

Ideally, a GFR measurement should have been performed in the population used to establish the cystatin C reference range, in order to assure that all test dogs truly had normal renal excretory function. However, the 99 dogs used to establish the reference range in this study had no medical complaints and were considered healthy based on physical and laboratory examinations. Further workup (including GFR) on healthy dogs would have also required a petition to the government for an animal experimentation permit. For these reasons, the authors opted to forgo simultaneous assessment of GFR. Standard convention was followed, and the reference range was based on the 0.025 and 0.975 quantiles, which excluded extreme values and decreased the likelihood of including dogs with early, undetected, chronic kidney disease.

Age, body weight, and gender did not influence cystatin C concentration, suggesting no need to calculate ranges dependent on these variables. These findings are similar to those of human studies, but contrary to those of one veterinary study. However, no GFR measurements were performed in that veterinary study, suggesting that the possible inclusion of early kidney disease could have impacted the results.

The authors observed low intraindividual cystatin C variation over time, which is an advantage for this test. Low intraindividual variation simplifies the collection of samples, which do not need to be drawn at any specific time of day.

Studies in dogs suggest that GFR increases significantly after protein ingestion. All dogs in this study were fasted, so the authors could not investigate the effects of food on cystatin C levels. In a human study, cystatin C remained relatively stable despite food consumption. However, a study in dogs demonstrated a significant decrease in cystatin C levels after feeding. This discrepancy might be explained by the different protein concentrations in human meals compared with those in dog food. More data are needed that examine the impact of feeding on serum cystatin C concentrations in dogs.

None of the dogs in this study had acute kidney disease. In people with acute kidney disease, serum cystatin C levels rise earlier than serum creatinine levels and correlate better with GFR. No published veterinary studies have analyzed serum cystatin C in the presence of acute kidney disease, but volume depletion might mimic this condition. Almy et al. showed that dogs with volume depletion had cystatin C concentrations within the reference range, despite a mildly reduced GFR. However, it is not known if volume depletion adequately reflects acute kidney disease. More studies are needed to investigate the influence of acute kidney disease, volume depletion, and postrenal azotemia on serum cystatin C concentration.

In this study, serum cystatin C correlated better with ECPC (r = -0.630; P < 0.001) than did serum creatinine (r = -0.572; P < 0.001), suggesting that cystatin C is probably a more sensitive test of reduced GFR. In other words, in dogs with early renal impairment, cystatin C concentrations will probably increase before serum creatinine concentrations. This is borne out in this study by the 76% sensitivity for detecting reduced GFR, which is 11% higher than that of serum creatinine. Although a sensitivity of 80% or 90% would be more desirable, currently no better test is available to diagnose early renal excretory dysfunction from a single canine blood sample.

Cystatin C and creatinine have similar positive predictive values. However, the higher negative predictive value for serum cystatin C (69%) compared with that of serum creatinine (62%) will result in fewer false negatives, suggesting a better screening test for early canine kidney disease.

The slightly better specificity of serum creatinine (91%) over serum cystatin C (87%) makes the authors reluctant to recommend complete replacement of serum creatinine testing at this time. Using both tests simultaneously should enhance diagnostic accuracy for kidney disease. The similar specificities for both parameters in this study suggest the need for additional studies that confirm the superior specificity of serum creatinine.

In this study, serum cystatin C was not influenced by neoplasia or infection. Although cystatin C is involved in inflammation and spread of cancer cells, studies in people have not found that these conditions alter serum concentrations; results of this current study agree. However, the authors examined only a limited number of dogs with neoplastic or infectious disease, suggesting that more data are needed to better assess the impact of these diseases on serum cystatin C concentration.

Conclusion
Endogenous, low-molecular-weight proteins could serve as a practical way to rapidly detect early kidney disease. Canine cystatin C was reliably measured with the human PET assay, independent of age, body weight, gender, or the presence of neoplastic/infectious disease. Serum cystatin C correlated slightly better with ECPC than did serum creatinine. Cystatin C had a higher sensitivity and negative predictive value than did serum creatinine, making it a better screening test for early canine kidney disease. The slightly better specificity of serum creatinine suggests that both cystatin C and creatinine should be measured simultaneously in order to enhance diagnostic accuracy for detecting (or excluding) canine renal excretory dysfunction.

Footnotes
a Particle-enhanced turbidimetric (PET) assay; Dako, Glostrup, Denmark
b Hitachi 911 automatic analyzer; Roche, Mannheim, Germany
c Creatinine anhydrous 5% solution; Sigma-Aldrich, Hamburg, Germany
d SPSS 13.0; SPSS Inc., Chicago, IL 60606

Acknowledgments
The authors thank Drs. Michael D. Willard and George E. Less for their contributions to the manuscript.

References


Primary Osseous Melanoma in the Tibia of a Dog

An 18-month-old, female Cane Corso dog was presented with a suspected primary tumor of the tibia. Plain radiographs and computed tomography (CT) of the tibia were highly suggestive of a primary bone neoplasm. A diagnosis of malignant melanoma was made by cytology. Total body survey radiographs, CT scan of the thorax, and abdominal ultrasound excluded the presence of neoplastic lesions other than in the tibia. Limb amputation was performed. Histology and immunohistochemical analysis of the tibial neoplasm confirmed the diagnosis of a melanoma with secondary metastasis to the popliteal lymph node. The dog was alive and in good physical condition 43 months after surgery. J Am Anim Hosp Assoc 2008;44:139-143.

Introduction

Osteosarcoma is the most common appendicular skeletal neoplasm in dogs, accounting for approximately 80% of canine primary bone tumors. Chondrosarcoma, fibrosarcoma, and hemangiosarcoma are reported to be the most prevalent nonosteoegenic primary tumors of the canine appendicular skeleton. Other reported primary tumors of bone are less common and include liposarcoma, lymphoma, myeloma, giant cell tumor of bone, and malignant fibrous histiocytoma. Primary appendicular skeletal neoplasms are more common in large breeds. Older dogs are generally affected, although a biphasic peak (2 and 9 years) has been reported for osteosarcoma.

Canine melanoma most frequently affects the oral cavity, mucocutaneous junctions, nail bed, skin, and eye. A poor prognosis is associated with the first three anatomical locations, due to local infiltration and development of distant metastases. Typically, primary cutaneous and ocular melanomas have a better prognosis than those in the oral cavity. In dogs, the development of distant metastases has been described for most internal organs, but metastases are more common in regional lymph nodes and lungs. In veterinary medicine, reports of bone metastasis from distant primary sites is limited, but prostate, mammary gland, and urinary bladder tumors are most often the sources of bone metastasis. Occasionally, metastases of melanomas to bone have been reported, but the authors are unaware of previous cases of primary osseous melanoma in dogs.

This report describes the clinical, radiological, and pathological findings in a dog with primary osseous melanoma.

Case Report

An intact female Cane Corso dog was evaluated at 11 months of age by a private practitioner for a moderate lameness of the right hind limb. Radiographs of the coxofemoral and stifle joints under general anesthesia were made and interpreted as normal. The dog was discharged with carprofen (2 mg/kg per os [PO] q 12 hours for 10 days). The lameness progressively worsened, and 6 months after initial presentation, the dog underwent reevaluation by the same practitioner. A painful 2 cm by 2 cm
swelling of the proximal tibia was noted. Nail beds and digits were clinically normal. No bone lysis of the phalanges was observed on radiographs made at that time. Based on radiographic findings, a primary osteosarcoma or an osteomyelitis was suspected. The dog was discharged with no therapy.

At 18 months of age, 30 days after the second evaluation, the dog was referred for a second opinion. On physical examination, the dog was severely lame, and a painful soft-tissue swelling (10 cm by 5 cm) of the right proximal tibia was found. Radiographic examination revealed an extensively lytic lesion associated with a pathological fracture of the tibial diaphysis, with disorganized periosteal proliferation. Transitional areas were enlarged and poorly defined (Figure 1).

A free-hand fine-needle aspiration biopsy from the lesion was performed with a 21-gauge needle. Clear fluid (2 mL) was collected and submitted for cytology. Cytological specimens were highly cellular and characterized by a population of pleomorphic cells. Cells were round to polygonal to spindle-shaped, and they were occasionally organized in highly cohesive groups. Cells had distinct borders and light-blue cytoplasm. Variable amounts of finely granular, black pigment (i.e., melanin) were present in cytoplasm. Nuclei were round with finely dispersed chromatin and one to two nucleoli. Rare atypical mitotic figures were present. Occasionally, atypical multinucleated giant cells (two to six nuclei) were detected. Foamy, reactive macrophages often containing coarsely clumped melanin (i.e., melanomacrophages) were also observed (Figure 2).

Based on cytology, a melanoma was diagnosed. To better evaluate the extent of the tumor, computed tomography (CT) was performed with a fourth-generation scanner. Transverse, 5-mm, contiguous slices of the right tibia were obtained. Pre- and postcontrast examinations, using a bolus intravenous (IV) injection of 600 mg/kg body weight of nonionic iodine contrast medium, were performed. Reformatted dorsal and sagittal planes were also obtained.

Regions of interest were drawn in the medullary cavity (i.e., center of the lesion), in the abnormal perilesional soft tissues, and in the muscle tissue not invaded by the neoplasm. Density attenuation data were measured before and after contrast medium administration. The CT study showed a space-occupying mass characterized by a precontrast mean attenuation value of 62.7 Hounsfield unit (HU). The mass was located mainly in the medullary cavity and invaded the surrounding tissues that were characterized by hypointenened areas (Figure 3A). The mass showed a strong contrast enhancement with a peak attenuation value of 161.5 HU. The contrast medium examination better demonstrated the heterogeneous soft-tissue swelling secondary to multifocal necrosis (Figure 3B).

A complete clinical examination was performed to exclude metastatic disease from a primary melanoma. The dog underwent ophthalmological, dermatological (including mucocutaneous junctions and nail beds), and oral cavity examinations. Clinical staging of the neoplasm included total body survey radiographs, CT scan of the thorax, and abdominal ultrasound. No paronychia, nail deformity, or nail loss were observed. No lesions other than in the tibia were detected. Amputation of the right hind limb at the coxofemoral joint was performed.

The entire leg, including the popliteal lymph node, was submitted for histopathological examination. No gross lesions were found in the skin, nails, or nail beds. Histology revealed severe and diffuse bone lysis with substitution and effacement of the compact bone and the medullary cavity by a densely cellular population of neoplastic cells. Cells were organized in nests and cords embedded in abundant fibrovascular stroma. Anisocytosis was prominent, and cells were round to spindle-shaped with distinct cell borders and
variably abundant, lightly eosinophilic cytoplasm. Variable numbers of cytoplasmic, black, fine granules were present in approximately 30% of the cells. Nuclei were round with finely dispersed chromatin and one to two magenta, round to triangular nucleoli. Mitotic figures ranged from zero to two per 400-magnification field. Multifocal necrosis and accumulation of melanomacrophages were evident [Figure 4]. A diagnosis of lightly pigmented, epithelioid-type melanoma was made. The popliteal lymph node was characterized by expansion of corticomедullary sinuses. One portion of the cortex was completely substituted by cohesive cells with similar morphology as the bone tumor. Immunohistochemical analysis was performed on the bone lesion and on the popliteal lymph node. Atypical cells stained positive for vimentin, neuron-specific enolase, S 100 protein, and Melan A protein [Figure 5]. Cells stained negative for cytokeratin, factor VIII, actin, and glial fibrillary acidic protein. These immunohistochemical findings were consistent with melanoma.

A final diagnosis of primary osseous melanoma with metastasis to the popliteal lymph node was made based on clinicopathological, ultrasonographic, and radiotomographic findings.

The dog rapidly improved after surgery and was discharged with a guarded prognosis. The owner refused adju-
vant chemotherapy for the dog. Regular follow-ups (every 4 months) included routine clinical examinations and chest and abdominal radiographs. The patient was alive and in good physical condition 43 months after surgery.

Discussion
This case seems to be the first report of primary bone melanoma in a dog.¹ The dog of this report survived for an extended period (at least 43 months). This is in contrast to the poor prognosis associated with malignant melanoma in the oral cavity or nail bed.³,⁵,¹²,¹³

Distant metastases of malignant melanoma are most frequently to regional lymph nodes and lungs.⁹ Secondary involvement of vertebrae, ribs, and radius has occasionally been documented in association with melanomas of the lips, eyes, and digits.³,⁹-¹²,¹⁴ In this dog, the main challenge was to define with certainty the primary intraosseous origin of the tumor. The main differential diagnosis was a primary nail bed melanoma.

Nail bed melanomas are generally diagnosed in dogs with a mean age of 9.3 years (range 5 to 13 years). The dog in this case was younger (1.5 years).¹⁵ The clinical findings considered typical of nail bed melanoma (such as paronychia, nail deformity, and nail loss)⁶ were not present in this case. Additionally, neither phalanx lysis nor digital masses were found. The long disease-free interval without adjuvant therapy documented in this case is unusual and is markedly different from what would be expected from other types of primary skeletal neoplasia. A long disease-free interval could have resulted from the so-called “tumor dormancy” that is well documented in humans and is described in a case of canine uveal melanoma.¹⁴,¹⁶-¹⁸

Hart hypothesized that malignant cells shed from the primary mass could remain dormant but viable, and that they could subsequently express their tumorigenic potential as a consequence of shifts in the balance between the host immune system and the tumor.¹⁷-¹⁹ However, the dog in the authors’ study had a disease-free interval of almost 3.5 years, while the reported case of uveal melanoma metastasized after 1.5 years.¹⁴

Primary osseous melanoma reported in humans may have a good prognosis.²⁰-²⁶ In the dog of this study, the tumor could have been derived from melanocytes of the endosteam. However, this hypothesis cannot be substantiated, since melanocytes have not been described in canine bone (although they have been identified in the endosteam of reptiles and birds).²⁷,²⁸ Another hypothesis for this unusual primary location could be the derivation from pluripotent bone marrow stem cells that are able to differentiate into melanocytic, adipocytic, osteocytic, and chondrocytic lineages.²⁹,³⁰ Moreover, cancer stem cells from human melanomas (called melanoma cells) have been demonstrated to differentiate into osteocytes, chondrocytes, or adipocytes. This further substantiates the hypothesis that stem cells and phenotypically distinct cancer cells may be related in some circumstances.²⁹-³¹ Another possible hypothesis in this case is that the lesion could have resulted from an inborn error of migration of melanocytes from the neural crest into the bone, with subsequent neoplastic transformation.

Conclusion
A primary tibial melanoma was diagnosed in a juvenile dog based on history and clinical and pathological examinations. Despite popliteal lymph node invasion, no other distant metastases developed 43 months after diagnosis. This case resembles primary osseous melanoma in humans.

Footnotes
¹ PQ2000S Philips MS; Philips Medical System S.p.A., Monza, Italy 20052

References
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Sézary Syndrome in a Cat

Sézary syndrome is an uncommon leukemic variant of cutaneous lymphoma in cats. This cat had recurrent dermatitis with erythematous, pruritic plaques. Multiple skin imprints and biopsy samples were obtained over a 6-month period, and histopathological findings were consistent initially with eosinophilic miliary dermatitis and later with erythema multiforme. One week before death, Sézary cells were identified in the peripheral blood that expressed cluster of differentiation (CD)3 and CD8 antigens. Massive infiltration of CD3+ lymphocytes was noted in the skin and multiple internal tissues by histopathological examination. This case demonstrates the difficulty in diagnosing cutaneous lymphoma early in the disease course.


Introduction

Sézary syndrome is a rare, end-stage leukemic variant of cutaneous T cell lymphoma (CTCL) and is characterized by the presence of small to large (8 to 20 µm) lymphocytes with cerebriform or convoluted nuclei (Sézary cells) in the peripheral blood in addition to erythematous skin lesions and peripheral lymphadenomegaly.1-4 Diagnosis of CTCL may be difficult, and the condition may mimic more common pruritic, exfoliative skin lesions. Multiple cutaneous biopsy samples may be necessary to obtain a definitive diagnosis.4

The cause of CTCL is unknown in cats. It has been reported, however, that feline leukemia virus (FeLV) could be isolated from tumor deoxyribonucleic acid (DNA) in a cat with cutaneous lymphoma while circulating antigen to FeLV was not detected.5 Humans with chronic atopic dermatitis may have an increased risk for developing CTCL, leading to speculation that chronic antigenic stimulation can lead to the development of CTCL, although the antigen in question is unknown.4,6

The purpose of this paper is to describe a feline case of Sézary syndrome that mimicked other clinical conditions, including eosinophilic miliary dermatitis and erythema multiforme, until thoroughly investigated postmortem.

Case Report

A 15-year-old, female spayed, domestic shorthair cat was presented for a recent onset of pruritic, crusty miliary dermatitis that occurred at multiple sites including the neck, dorsum, and inner thighs. Cytological examination of skin imprints revealed many degenerate neutrophils containing bacterial cocci. Additional skin scrapings for mites and a Wood’s lamp test for dermatophytes were negative. The cat was discharged on Clavamox (amoxicillin and clavulanate potassium, 62.5 mg per os [PO] q 12 hours for 2 weeks) for the bacterial pyoderma.

Two months later, the cat was assessed by a board-certified veterinary dermatologist and was clinically described to have multifocal areas of erythema, alopecia, and crusting on the dorsum along with erythema, erosion, and excoriations on the medial thighs and paronychia. Increased numbers of neutrophils and eosinophils with few round cells were evident.
on cytological examination of skin imprints, with eosinophils predominating [Figure 1]. Staining the preparations with a modified Wright’s stain\(^a\) rather than Dip Stain\(^b\) more clearly revealed the round cells as a mixture of poorly granulated mast cells and lymphocytes. A combined enzyme-linked immunosorbent assay (ELISA) for FeLV and feline immunodeficiency virus (FIV) was performed on whole blood and determined to be negative.\(^c\) The results of a complete blood count (CBC) and serum biochemical panels performed were within reference intervals. A culture on hair samples for dermatophytes was performed and exhibited no growth. *Streptococcus* spp. (beta hemolytic) and *Staphylococcus aureus* were isolated from a skin swab. Because of the antibiotic sensitivity results, the presence of secondary pyoderma, and possible gastrointestinal irritation from Clavamox, the antibiotic was switched to clindamycin (25 mg PO q 12 hours). To help with the intense pruritus, clemastine (1.34 mg; half tablet PO q 12 hours) was also initiated. Histopathological examinations of skin samples taken from the trunk and thigh revealed multifocal, erosive, suppurative dermatitis with bacterial colonies, epidermal necrosis, and mast cell infiltrate—consistent with hypersensitivity or miliary dermatitis with secondary pyoderma.

One month later, the cat’s skin condition had not resolved, despite the continued administration of clindamycin. Concern about the possibility of cutaneous lymphoma as the cat’s underlying problem led to the collection of a second set of skin biopsy samples, which revealed a similar histological diagnosis. Complete blood count and serum biochemical panels were repeated with no abnormal results noted. As an adjunctive treatment for the intense pruritus, the cat received an injection of 15 mg of Depo Medrol (methylprednisolone acetate, 20 mg/mL) subcutaneously, which resulted in slight improvement of the skin lesions for about 7 to 10 days. Because food allergies can cause cutaneous manifestations of a hypersensitivity response, the cat was started on a food trial using Innovative Veterinary Diets,\(^d\) which also was believed to result in mild clinical improvement for a short time.

Four months after the initial presentation, and despite being on a food trial, the cat’s dermatitis worsened. It involved most of the skin of the dorsum and ventrum, leading to almost complete hair loss over the ventrum, inner thighs, and forelimbs. Patchy alopecia was present over the dorsum. Skin-punch biopsy samples were collected and revealed continued presence of eosinophilic and mastocytic dermatitis. Evidence of individual necrotic keratinocytes within all layers of the epidermis and follicular epidermis was suggestive of erythema multiforme \(^e\) [Figure 2]. Lymphocytic infiltrates were also evident in the epidermis and follicular epidermis \(^f\) [Figure 2]. As a result of this diagnosis and the concern of clindamycin-induced erythema multiforme, the treatment was switched to enrofloxacin (22.7 mg; one tablet PO q 24 hours for 14 days) and a daily injection of dexamethasone sodium phosphate (1 mg) subcutaneously for 1 week, followed by tapered doses at every 3-day intervals. The cat responded well to the treatment within 2 weeks. By 5 months after the initial visit, the majority of the skin lesions had resolved, hair had regrown, and pruritus had decreased. A few crusty lesions remained, principally around the neck and head. Over the next several months, the cat was treated periodically with antibiotics previously mentioned for recurrent pyoderma. Oral dexamethasone (1 mg q 3 days) was administered for intermittent pruritus.

Ten months following the initial examination, the cat’s general condition deteriorated markedly. Physical examination revealed severe, generalized, moist erythematous dermatitis; dehydration; and slight bilateral, popliteal
lymphadenomegaly. Cytological assessment of skin imprints revealed numerous round cells that resembled medium-sized lymphocytes containing abundant, azurophilic, cytoplasmic granules.

A CBC showed a leukocytosis (27,700/µL, reference interval 5500 to 19,500/µL) characterized by a neutrophilia with a left shift (segmented neutrophils 11,400/µL, reference interval 2500 to 12,500/µL; band neutrophils 5000/µL, reference interval 0 to 300/µL); lymphocytosis (9700/µL, reference interval 2000 to 7000/µL); basophilia (300/µL, reference interval 0 to 100/µL); and normocytic, normochromic anemia (packed cell volume 28%, reference interval 30% to 45%). Examination of the peripheral blood film demonstrated toxic changes in neutrophils and increased numbers of lymphocytes with oval to lobulated nuclei and azurophilic, cytoplasmic granules [Figure 3A]. Occasional cells had cerebriform nuclei resembling Sézary cells [Figure 3B]. Toxic changes in the neutrophil series included diffuse cytoplasmic basophilia, Döhle bodies, and occasional asynchronous nuclear maturation.

Leukocytes in the peripheral blood were immunophenotyped using a previously described method and a panel of monoclonal antibodies to T lymphocyte subsets (i.e., CD4, CD8), B lymphocytes (i.e., CD21), and monocytes (i.e., CD14). The percentages of leukocytes that expressed CD4, CD8, CD21, and CD14 of the total population were 1%, 85%, 10%, and 4%, respectively. These findings indicated that CD8+ T cells contributed to the peripheral lymphocytosis.

The lack of finding CD4+ T lymphocytes in an inflammatory leukogram was unusual and suggested a clonal proliferation of CD8+ T cells, which was confirmed 2 weeks later with a polymerase chain reaction (PCR) assay for T cell antigen-receptor gene rearrangement of the peripheral blood. However, this information was not known at the time the CBC results were reported. The presence of a neutrophilia with a left shift could be explained by chronic inflammation of the skin. Lymphocytosis with abnormal granular lymphocytes seen in this cat was consistent with a lymphoproliferative disorder or reactive lymphocytosis.

A serum biochemical profile was performed and revealed the following abnormalities: increased urea nitrogen (64 mg/dL, reference interval 17 to 35 mg/dL), hyperglobulinemia (5.9 g/dL, reference interval 2.6 to 4.8 g/dL), increased alanine transaminase (ALT) activity (184 U/L, reference interval 27 to 127 U/L), and hyperbilirubinemia (total 2.1 mg/dL, reference interval 0.0 to 0.4 mg/dL). The azotemia was attributed to decreased glomerular filtration rate secondary to dehydration. The increased ALT activity indicated hepatocellular damage, and hyperbilirubinemia was thought to indicate cholestasis. Hyperglobulinemia was likely caused by chronic inflammation of the skin.

The cat died 3 days later, before any further clinical assessment or diagnostics could be completed.

A necropsy was performed, and gross examination revealed diffuse, 2- to 3-mm, cutaneous papules located over the dorsum, with a normal distribution of hair.
However, on the ventrum and medial surfaces of all four limbs, hair loss was almost complete and accompanied by a uniform, thick, serous exudate that varied in appearance from bright red to yellow. The left prescapular lymph node was enlarged (1.5 by 1.0 by 1.0 cm). All other organs appeared grossly normal, including the liver, kidney, and spleen. Histopathological examination of affected skin revealed diffuse infiltration of the dermis, adnexa, and epidermis, with a population of neoplastic round cells. The neoplastic round cells ranged in size from 10 to 20 µm, with indistinct cell borders and scant, pale, eosinophilic cytoplasm. Nuclei were round, centrally located, and measured 10 to 15 µm with hyperchromatic, coarsely stippled chromatin. Mitotic figures averaged 1 per high-power field (40× objective). Moderate numbers of mast cells were intermixed with neoplastic cells in the dermis. Neoplastic cells in the skin stained positively for CD3 [Figure 4A] and negatively for CD79a [not shown]. Multifocal areas of epidermal ulceration, neutrophilic crusting with moderate numbers of cocci, and follicular casts were also present.

**Discussion**

Identifying the neoplastic lymphocytes in the skin, left prescapular lymph node, kidney, liver, and spleen as positive for CD3 (a mature T cell surface marker) and the presence of these neoplastic lymphocytes within the epidermis led to a diagnosis of epitheliotropic CTCL. Furthermore, immunophenotyping and PCR assay for antigen-receptor gene rearrangement of the lymphocytes in the blood subclassified the T cells as a clonal population of CD8+ cells. To the authors’ knowledge, this is the first case of Sézary syndrome in a cat in which the Sézary cells were identified as CD8+ T cells with a clonal rearrangement of the T cell antigen receptor.

Cutaneous T cell lymphoma in humans is usually characterized by an elevated dermal CD4+/CD8- ratio and the presence of a T cell clone detected by PCR in tissues and peripheral blood.

In humans with Sézary syndrome, the cells are most commonly reported as CD4+ T cells, whereas cases that express CD8 are less common. It is possible that this cat had an unusual form of Sézary syndrome in which a proliferation of CD8+ rather than CD4+ lymphocytes was present. However, more cases of Sézary syndrome in cats will need to be immunophenotyped to determine if the cell type is more commonly CD4+, as it is in humans.

In this cat, frequent lymphocytes were noticed in the mixed inflammatory cell population of the skin imprints and in the epidermis upon histopathological examination of some skin biopsy samples. However, hypersensitivities to various antigens can cause nonmalignant accumulation of lymphocytes in the skin, and early in the course of CTCL, the infiltrative lymphocytes are usually reactive T cells.10,11

![Figure 4A](image-url) — Skin of ventrum; cat. Immunohistochemical staining for CD3 expression on lymphocytes that infiltrate the dermis and epidermis (Ventana Red detection kit, Mayer’s hematoxylin counterstain, bar=60 µm).

![Figure 4B](image-url) — Liver; cat. Eosinophils comprise the majority of infiltrating cells in the sinusoids (Hematoxylin and eosin stain, bar=70 µm).
Histologically, it can be nearly impossible to differentiate benign inflammatory skin diseases from early CTCL. Erythema multiforme, diagnosed earlier in the disease course by histopathological examination of skin biopsy samples, is also characterized by invasion of the epidermis by T cells (usually CD8+), leading to keratinocyte apoptosis. The earlier diagnosis of erythema multiforme was also supported by the administration of various antibiotics (clindamycin) that have been associated with the development of erythema multiforme, and by apparent partial resolution of most of the skin lesions for a few months after removal of the suspected offending drug. It is possible that the slow progression of disease seen in this case contributed to the lack of an earlier, more specific diagnosis.

The prominence of eosinophils may be explained by the presence of Th2 lymphocyte cytokines (e.g., interleukin [IL]-3, IL-4, or IL-5) that stimulate growth and differentiation of eosinophils. In humans, Sezary syndrome and hypereosinophilia are associated with increased Th2 cytokines and are related to the progression of the lymphoma malignancy. Rare, paraneoplastic, hypereosinophilic syndromes have been described in horses and dogs that have concurrent lymphoma; however, cytokine production in these disorders has not been defined. The cause of sudden death in this cat is unknown. Death in cats and dogs with CTCL is reported to be most commonly caused by septicemia or metastatic lymphoma. Humans with CTCL frequently succumb to fatal opportunistic infections.

**Conclusion**

This case report is an example of Sezary syndrome, a rare, end-stage leukemic form of CTCL. This report is unique in that it demonstrates CD8+ Sézary cells in a cat.

**Footnotes**

a Richard Allen Scientific, Kalamazoo, MI 49008
b Volu-Sol, Inc., Salt Lake City, UT 84121
c IDEXX Laboratories, Westbrook, ME 04092
d Royal Canin USA, Inc., St. Charles, MO 63301
e Cell-Dyn 3700; Abbott Laboratories, Abbott Park, IL 60064-3500
f Southern Biotechnology, Birmingham, AL 35260
g Serotec, Raleigh, NC 27604-1699
h Boehringer Mannheim/Hitachi 911, Indianapolis, IN 46250
i Rabbit antihuman; DAKO, Carpintera, CA 93013
Ventana Red detection kit; Ventana Medical Systems, Inc., Tucson, AZ 85755
j HM57; DAKO, Carpintera, CA 93013

**Acknowledgments**

The authors acknowledge Drs. Marjorie Arzter, Susan Nelson, and Laura Garrett for their care of the animal and their contributions to this case; Dr. Mehrdad Ameri for immunophenotyping the peripheral blood; Dr. Anne Avery for the PCR testing; and Cindy Chard-Bergstrom for the immunohistochemical testing.

**References**

Primary Tracheal Collapse in a Cat

A 7-year-old, neutered male, domestic shorthair cat was presented for severe inspiratory dyspnea of 2 to 3 days’ duration. Radiography and tracheobronchoscopy confirmed the diagnosis of primary extrathoracic tracheal collapse. The cat was treated with oxygen, dexamethasone, and terbutaline, but no improvement was seen. Surgical correction was performed using nine prosthetic tracheal ring implants. Clinical signs improved after surgery, and the cat continued to do well 11 months after surgery, despite development of unilateral laryngeal paralysis. J Am Anim Hosp Assoc 2008;44:149-153.

Case Report

A 7-year-old, neutered male, domestic shorthair cat was presented for persistent dyspnea of 2 to 3 days’ duration. Abnormalities on physical examination at presentation included increased inspiratory effort and tachypnea. A cough was easily elicited on palpation of the extrathoracic trachea. No abnormalities were noted on auscultation of the heart and lungs. Thoracic radiographs indicated narrowing of the tracheal lumen at the junction of the thoracic inlet on inspiration, with no evidence of extraluminal compression [Figure 1]. The cat was placed in a 40% oxygen cage and given dexamethasone (0.2 mg/kg intravenously [IV]).

Hematological and serum biochemical analyses performed the next day revealed a mature neutrophilia ($15.326 \times 10^3/\mu$L, reference range 1.1 to $10.4 \times 10^3/\mu$L), lymphopenia ($0.316 \times 10^3/\mu$L, reference range 1.5 to $7 \times 10^3/\mu$L), eosinopenia ($0 \times 10^3/\mu$L, reference range 0.037 to $0.914 \times 10^3/\mu$L), hyperglycemia ($223 \text{mg/dL}$, reference range 59 to 124 mg/dL), hyperproteinemia ($8.3 \text{g/dL}$, reference range 6.5 to 7.7 g/dL), hyperglobulinemia ($4.9 \text{g/dL}$, reference range 2.5 to 4.7 g/dL), and hypocholesterolemia ($76 \text{mg/dL}$, reference range 101 to 409 mg/dL). The hematological changes and hyperglycemia were attributed to stress. The mild elevation in globulins and the hypocholesterolemia were considered incidental findings. Results of feline immunodeficiency virus and feline leukemia virus tests were negative.

Anesthesia was induced with propofol (6 mg/kg IV) and maintained with isoflurane. Laryngeal examination performed before intubation revealed no evidence of pharyngeal or laryngeal masses. Arytenoid abduction was within normal limits. The nasopharynx was normal on retroflex examination. An endotracheal tube was then placed to maintain general anesthesia. Tracheobronchoscopy revealed a normal tracheal lumen for the first 20 cm of the trachea (measured from the upper canine teeth), with collapse along the dorsal membrane thereafter [Figure 2]. The distal luminal diameter was decreased by approximately 75% and was classified as a grade III collapse.\(^1\) Beyond the thoracic inlet, the diameter of the trachea appeared within normal limits, and the main-stem bronchi were identified. Esophagoscopy revealed no evidence of extraluminal compression, suggesting a diagnosis of tracheal collapse.

Over the following 2 days, the cat remained in an oxygen (40%) cage, and dexamethasone treatment was continued. Diazepam (0.37 mg/kg IV) and butorphanol (0.2 mg/kg IV) were administered as needed for
increased respiratory difficulty or increased anxiety. An oral suspension of terbutaline (0.03 mg/kg per os [PO] q 8 hours) was started on day 3 of hospitalization in an attempt to induce bronchodilation. The cat’s clinical signs continued to worsen despite medical management, and the owners elected surgery on day 4.

The cat was anesthetized using the previously described protocol and was prepared for surgery. The skin and subcutaneous tissues along the ventral cervical midline were incised from the larynx to the manubrium. The sternohyoid and sternocephalicus muscles were separated along their midline to expose the cervical trachea. The recurrent laryngeal nerves were identified, protected, and retracted away from the trachea. The peritracheal tissues were dissected, creating a tunnel immediately around the specific areas of the trachea that were to be fitted with prosthetic rings. Nine prosthetic rings (each 1 cm wide) were placed around the trachea about 5 to 8 mm apart. The rings had been constructed from 3-mL syringe cases and fenestrated in four places to allow suture placement. The first tracheal prosthesis was placed 1 cm distal to the larynx, and the last was placed at the thoracic inlet. A curved hemostat was used to guide and position each ring around the trachea. The open end in each ring was positioned on the ventral aspect of the trachea, and the rings were then secured ventrally, laterally, and dorsally with 4-0 polypropylene sutures. Sutures were directed around rather than through the cartilages, with at least one of the sutures for each ring engaging the trachealis muscle. Cranial traction on the prosthesis allowed one ring to be placed at the thoracic inlet. After each ring was placed, the endotracheal tube was manipulated to ensure it had not been sutured to the trachea. Specimens for bacterial culture were obtained from several of the prosthetic rings before closure.

The sternohyoid and sternocephalicus muscles were apposed with simple continuous sutures of 3-0 polydioxanone (PDS), and the subcutaneous tissues were closed in the same fashion. The dermis was closed with a continuous intradermal pattern using 4-0 PDS. Cruciate sutures were then placed using 3-0 nylon.

Tracheobronchoscopy was performed immediately after surgery. The trachea was erythematous, with a small amount of blood visible within the lumen. The scope was advanced 13 to 15 cm caudal to the nares. Narrowing of the tracheal lumen was minimal as far distally as could be visualized. The suture material used to secure the prosthetic rings could be seen within the lumen. The bronchi appeared normal, with no evidence of collapse. A 25-µg fentanyl patch was placed postoperatively for analgesia.

The cat recovered well from anesthesia and surgery. Oral amoxicillin-clavulanate (12 mg/kg q 12 hours) was administered for 2 weeks after surgery. Bacterial cultures of tracheal specimens taken at surgery were negative. Thoracic radiographs taken before discharge showed a 100% increase in the diameter of the tracheal lumen compared with the size of the lumen on radiographs taken at initial presentation [Figure 3]. By the time of discharge 7 days after surgery, the clinical signs of tracheal collapse had markedly improved. Two months later, the owners reported the cat was doing well with minimal coughing.

The cat returned 1 month after surgery for reevaluation. The owners reported no respiratory difficulty, coughing, heat intolerance, or exercise intolerance since the surgery, but they had noticed a change in voice. A laryngeal examination performed under light sedation revealed right-sided laryngeal paralysis. This complication was attributed to damage to the recurrent laryngeal nerve that was likely secondary to retraction during surgery, despite the authors'
attempts to protect the nerve. During tracheobronchoscopy, suture material could be seen intermittently in the tracheal lumen from 9.5 cm caudal to the upper canines to the thoracic inlet [Figure 4]. Redundant dorsal membrane was evidenced in the distal trachea, but overall, the tracheal diameter appeared normal.

Discussion

Tracheal collapse is described as a dorsoventral flattening of the tracheal rings with concurrent laxity of the dorsal tracheal membrane.\(^1\)\(^{-5}\) It is diagnosed most commonly in middle-aged toy and small-breed dogs, but it has also been reported rarely in cats, calves, pigs, horses, and goats.\(^6\) Clinical signs are often exacerbated by heat, excitement, and eating or drinking. A history of chronic coughing, exercise intolerance, and dyspnea is common in canine patients; coughing is less common in feline patients. Feline cases are typically secondary to intra- or extraluminal obstruction caused by tumors, trauma, or congenital abnormalities.\(^7\)\(^8\)

Definitive diagnosis of tracheal collapse requires imaging studies and/or tracheobronchoscopy. Plain radiographs have been shown to be diagnostic in 59\% of canine cases.\(^2\)\(^8\) Lateral views of the thorax should be obtained during both inspiration and expiration. Inspiratory films best demonstrate collapse of the cervical trachea, while expiratory films demonstrate collapse of the main-stem bronchi or intrathoracic trachea.\(^1\)\(^2\) Other noninvasive techniques, such as fluoroscopy and ultrasonography, can provide diagnostic support when thoracic radiographs alone are insufficient.\(^3\) Fluoroscopy can be beneficial in identifying collapse of the main-stem bronchi, which is not often evident on thoracic radiographs.\(^1\) Fluoroscopy is also a dynamic study that is performed in a conscious animal and allows identification of tracheal collapse during active coughing.\(^8\) Regardless, tracheobronchoscopy remains the most sensitive and specific diagnostic method, and it is the method of choice for visualizing the dorsal tracheal ligament and tracheal mucosa.\(^2\)\(^3\) In addition, the tracheal mucosa and secretions can be evaluated, and samples for cytology and bacteriology can be collected. The animal should be lightly anesthetized before tracheoscopy to allow evaluation of swallowing reflexes and laryngeal function.\(^1\)

Although the inciting cause of tracheal collapse has not yet been determined, it is known that this condition is associated with a defect in the tracheal cartilage that results in loss of rigidity.\(^2\) In some dogs with tracheal collapse, the tracheal cartilage is hypocellular with less chondroitin sulfate and calcium than normal tracheal cartilage.\(^5\) It has been postulated that both the abnormal cartilage and the aging process play a role.\(^9\)

Tracheal collapse can be managed medically or surgically, but neither treatment is curative. Medical management most often includes some combination of weight loss, antibiotics, antitussives, bronchodilators, antiinflammatories, and treatment of the underlying cause (if identified).\(^1\) Medical treatment of an animal with acute tracheal collapse and dyspnea should include oxygen.

Specimens collected from the trachea for cytology and culture can be used to guide antibiotic therapy and to diagnose bacterial infection or allergic tracheitis that could be the initiating cause of tracheal collapse. Positive tracheal cultures have not been associated with cytological evidence of infection or inflammation, which suggests that antimicrobial therapy is not necessarily indicated in the treatment of tracheal collapse.\(^10\) Organisms other than *Bordetella bronchiseptica* may be normal tracheal flora.

Antitussives are commonly recommended in dogs to reduce irritation and epithelial damage caused by chronic coughing. Coughing perpetuates collapse by initiating...
inflammation, which increases mucous production and decreases mucociliary clearance. Bronchodilator treatment is controversial and appears to improve large-airway collapse by minimizing small-airway obstruction and thereby reducing intrathoracic pressure. Terbutaline was added to the treatment regimen of this cat to reduce intrathoracic pressure and potentially prevent large-airway collapse despite absence of small-airway disease.

Surgical treatment is recommended when the animal is not responding to medical therapy or when the quality of life has diminished. Many surgical options for tracheal collapse have been described, including tracheal ring chondrotomy, plication of the dorsal tracheal membrane, tracheal resection and anastomosis, and intraluminal or extraluminal tracheal prostheses. Most of these techniques have not been successful, but extraluminal prostheses (spiral or total ring) have had the most success. Some surgeons prefer spiral prostheses over complete-ring prosthetics because of reports of improved flexibility and support of the trachea, as well as uniform contact of the spiral prostheses and the trachea. Also, in a ventral approach through the cervical midline, the spiral prosthesis can be placed further into the thorax than the complete-ring prosthesis. Spiral prostheses have been associated with tracheal necrosis due to extensive soft-tissue dissection, but newer surgical approaches have been described to help avoid this complication.

Placement of prosthetic rings generally reduces clinical signs by 75% to 85%, with the most common postoperative complications being laryngeal paralysis, coughing, and dyspnea. Laryngeal paralysis is most often caused by trauma to the recurrent laryngeal nerve during surgery. Tracheal necrosis can occur in the days after surgery if the tracheal blood supply is damaged during the procedure.

Since 1974, six cases of intratracheal obstruction or neoplasia have been reported in cats, but only two of these cases had evidence of secondary tracheal collapse. In these two cases, tracheal collapse was cranial to the thoracic inlet and caudal to an intraluminal obstructing lesion. Squamous metaplasia was the primary cause of collapse in one of these cats, and a congenital abnormality with granulomatous changes was the primary cause of collapse in the other. In 1991, a case of tracheal collapse in a cat was reported secondary to suspected trauma, and surgical correction using a spiral-cut prosthesis was successful. The authors are unaware of any previous reports of successful surgical correction of primary tracheal collapse in a cat. The signalment in this case was atypical, because primary tracheal collapse is not common in cats, and this cat had no history of prior or progressive clinical signs. No signs of an inciting cause were identified on radiography, laryngeal examination, tracheobronchoscopy, or esophagoscopy. No gallop rhythm or heart murmur was auscultated in this cat, although echocardiography would be required to exclude concurrent heart disease. The acute onset of signs after being outdoors is more consistent with trauma, allergies, or toxins, although none could be identified. It is plausible that heat stress could have contributed to the acute onset and exacerbated the weakened dorsal tracheal membrane. Multiple radiographic images of the thorax were obtained to exclude other disease processes. Ideally, both inspiratory and expiratory thoracic radiographs should have been obtained, but they were not in this case because of the cat’s respiratory distress upon initial presentation. The diagnosis in this case was based on tracheobronchoscopy, which revealed the redundant dorsal tracheal membrane that is consistent with tracheal collapse in small-breed dogs.

The cat’s condition continued to worsen in the hospital with medical management alone, and increasingly frequent sedation was required to decrease anxiety and ease respiratory effort. Medical management with corticosteroids was ultimately insufficient, and the decision for surgery was a final attempt at treatment. The surgical approach and procedure were identical to those reported for repair of collapsing trachea in dogs, and they effectively reduced clinical signs in this cat. The surgeon chose individual, polypropylene rings as prostheses. Intraluminal stents were not used, because the surgeons were not experienced using this new modality at the time. In addition, intraluminal stenting was associated with many complications and was not a widely accepted procedure at the time.

Conclusion

Primary tracheal collapse is diagnosed most commonly in toy and small-breed dogs, but cats can also be affected. A history of exercise intolerance and dyspnea in feline patients should prompt airway evaluation via radiography, fluoroscopy, or tracheobronchoscopy. Although most reported cases of tracheal collapse in cats have been secondary to other disease processes such as neoplasia, primary tracheal collapse should also be considered. Surgery using extraluminal prostheses seems to be a viable option for correction of primary tracheal collapse in cats.

Acknowledgments

The authors thank TC Coffman and Drs. Michelle Fabiani and Derek Burney for their contributions.

References