

# Evaluation of survival time in dogs with stage III osteosarcoma that undergo treatment: 90 cases (1985–2004)

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## ABBREVIATIONS

NSAID Nonsteroidal anti-inflammatory drug

**Objective**—To assess survival time in dogs that underwent treatment for stage III osteosarcoma and evaluate factors affecting survival.

**Design**—Retrospective case series.

**Animals**—90 dogs with stage III osteosarcoma.

**Procedures**—Records in the osteosarcoma database at the Animal Cancer Center at Colorado State University from 1985 to 2004 were searched for dogs with metastatic disease at the time of evaluation. Dogs were included in the study if they had metastasis to any site and if treatment was initiated. A Kaplan-Meier survival analysis was performed, and the influences of age, sex, breed, primary tumor site, metastatic sites, and treatment on outcome were analyzed via log-rank analysis.

**Results**—Median survival time was 76 days, with a range of 0 to 1,583 days. No significant differences in survival times on the basis of age, sex, breed, or primary site were observed. Breeds and primary tumor sites were typical of those usually associated with osteosarcoma in dogs. Dogs treated palliatively with radiation therapy and chemotherapy had a significantly longer survival time (130 days) than dogs in all other treatment groups. Dogs treated with surgery alone had a significantly shorter survival time (3 days) than dogs treated with surgery and chemotherapy (78 days). Dogs with bone metastases had a longer survival time than dogs with soft tissue metastases.

**Conclusions and Clinical Relevance**—Treatment of dogs with stage III osteosarcoma can result in various survival times. Dogs with metastasis to bone and dogs that were treated palliatively with radiation and chemotherapy had the longest survival times. (*J Am Vet Med Assoc* 2006;228:1905–1908)

Neoplastic disease in dogs that are examined because of osteosarcoma is often staged on the basis of 3-view thoracic radiographic imaging (left, right lateromedial, and ventrodorsal radiographic views of the thorax) and nuclear scintigraphy to rule out the presence of gross metastases prior to initiating treatment. Approximately 10% of dogs have gross pulmonary or bone metastases at the time of initial exam-

ination. The diagnosis of osteosarcoma with metastatic disease is associated with a grave prognosis. We observed that certain dogs with metastatic disease lived longer than expected with aggressive treatment; the decision to initiate treatment was often made at the owner's request, despite the poor odds of survival. The purpose of the study reported here was to assess survival times in dogs in which a diagnosis of stage III osteosarcoma was made at the time of initial examination and that underwent treatment and to determine prognostic factors for improved survival times in affected dogs.

## Criteria for Selection of Cases

The osteosarcoma database maintained by the Animal Cancer Center at Colorado State University was searched to identify and retrospectively evaluate records of dogs from 1985 to 2004 that had stage III osteosarcoma at the time of initial examination at the teaching hospital. The database included approximately 1,500 records of dogs with osteosarcoma examined during this time. Records were excluded from the study if the dogs had been euthanized with no treatment after diagnosis (13 cases) or were lost to follow up (10 cases). Dogs that died shortly after initiation of treatment were included in the study.

## Procedures

Stage III osteosarcoma was defined as osteosarcoma that had metastasized to any site. Bone metastases were identified by means of nuclear scintigraphic imaging, radiographic imaging, or both. Diagnosis of pulmonary metastases was made on the basis of 3-view radiographic series of the thorax. Survival time was defined as the number of days the dog lived after the date of diagnosis. The Kaplan-Meier product limit method was used to determine outcome data. Outcome data were compared on the basis of primary tumor site, site of metastasis, treatment, age, sex, and breed by use of log-rank analysis.<sup>a</sup>

## Results

Records of 90 dogs were available for analysis, representing 6% of the dogs with osteosarcoma examined at the veterinary teaching hospital during that time. Survival times ranged from 0 to 1,583 days. Median survival time was 76 days. The 1-, 2-, and 3-year survival rates were 6.6%, 4.7%, and 3.5%, respectively.

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Treatments included combinations of chemotherapy, surgery, radiation therapy, administration of bisphosphonates, and administration of NSAIDs. The goal of surgery was generally radical or wide excision of the primary tumor by limb-sparing, amputation, or hemipelvectomy procedures. One dog underwent amputation and thoracotomy for pulmonary metastectomy, and 1 dog with primary lung osteosarcoma underwent thoracotomy for lung lobe resection. Various chemotherapy protocols were administered. In all instances, dogs were treated with cisplatin or carboplatin, doxorubicin, or a combination of doxorubicin and cisplatin or carboplatin. In all dogs treated with radiation therapy, the treatment goal was to provide palliative care. Dogs were assigned to 1 of 6 treatment groups for analysis; groups were NSAID-opioids (dogs received an NSAID, an opioid, or both;  $n = 3$  dogs), surgery alone (10), surgery and chemotherapy (27), radiation alone (26), radiation and chemotherapy (22), and chemotherapy alone (2).

Comparisons among groups on the basis of age, breed, sex, and primary tumor site yielded no significant differences. Breeds represented were consistent with those previously reported for osteosarcoma, and the breeds represented most frequently were mixed breed ( $n = 16$  dogs), Rottweiler (14), Labrador Retriever (10), Golden Retriever (9), and Great Dane (5). Median age at the time of initial examination at the teaching hospital was 8.5 years. More than half of the dogs were 6 to 9 years old. Forty-nine dogs were females, and 41 were males; 2 dogs were sexually intact females, and 13 were sexually intact males. Primary tumors were most frequently diagnosed in a long bone, with 21 tumors involving the proximal portion of the humerus, 18 involving the distal portion of the radius, 14 involving the tibia, 12 involving the femur, 7 involving the ulna, and 4 involving the scapula. In 2 dogs each, the vertebral column, rib, and pelvis were involved, and in 1 dog each, the body wall, mandible, maxilla, nasal cavity, lung, fibula, retroperitoneal space, and a phalanx were involved.

Sites of metastasis included the lung alone ( $n = 38$  dogs), lung and other sites (5), bone (36), lymph node (8), and other sites (3; **Table 1**). Median survival times for dogs with metastasis to the lung alone and to the lung and other sites were 59 and 19 days, respectively. Median survival time for dogs with metastasis to the lymph nodes was 57 days. Median survival time for dogs with metastasis to bone was 132 days. Dogs with metastasis to the bone had a significantly longer survival time, compared with those with metastasis to lung ( $P = 0.003$ ), lung and another site ( $P = 0.002$ ), and lymph node ( $P = 0.001$ ). The 6 dogs that survived the longest (ie, from 359 to 1,583 days) all had metastasis to long bones with no evidence of pulmonary metastases.

The treatment group with the longest survival time was the group that received radiation and chemotherapy, with a median survival time of 130 days (**Table 2**). This was significantly longer than the median survival times of dogs in the groups treated with NSAID-opioids ( $P = 0.026$ ), surgery alone ( $P = 0.004$ ), surgery and chemotherapy ( $P = 0.035$ ), and radiation alone ( $P = 0.017$ ). Dogs that were treated

Table 1—Summary of median survival time (MST) according to site of metastasis in 90 dogs with stage III osteosarcoma that were evaluated in a retrospective case series.

Metastatic site	No. of dogs	MST (d)
Lung	38	59
Lung and another site	5	19
Bone	36	132
Lymph node	8	57
Other	3	78

Table 2—Summary of MST according to treatment group in the same dogs as in Table 1.

Treatment group	No. of dogs	MST (d)
NSAID-opioids	3	35
Surgery alone	10	3
Surgery and chemotherapy	27	78
Radiation alone	26	64
Radiation and chemotherapy	22	130
Chemotherapy alone	2	37

with chemotherapy alone had a median survival time of 37 days, a finding that was not different from survival times in the other groups, but this was likely a result of small sample size.

Median survival time in dogs treated with surgery and adjuvant therapy was significantly ( $P = 0.004$ ) longer, compared with that in dogs treated with surgery alone. Median survival times in those 2 groups were 78 and 3 days, respectively. Five of the 10 dogs that were treated with surgery alone died acutely in the perioperative period because of complications of anesthesia or postoperative cardiac arrest and lived either 0 days (4 dogs) or 3 days (1 dog) after diagnosis. Those dogs all had primary long-bone osteosarcoma with metastasis to the lung (4 dogs) or lymph node (1 dog).

## Discussion

Survival times in dogs treated for stage III osteosarcoma vary; in the present study, survival time ranged from 0 to 1,583 days, with a median survival time of 76 days. However, a small number of dogs survived much longer than expected. Two groups of dogs with stage III osteosarcoma had significantly longer survival times: dogs treated with palliative radiation therapy and chemotherapy (median survival time, 130 days) and dogs that had metastasis to bone with no pulmonary metastases (132 days). Although those 2 groups of dogs had similar median survival times and there was overlap of dogs between groups, the 2 groups were not identical. Our finding that dogs with bone metastases lived longer than dogs with soft tissue metastases was contrary to findings reported in humans with osteosarcoma.<sup>1</sup> In that study, patients that had stage III osteosarcoma with bone metastases had shorter survival times, compared with patients that had lung metastases. That finding may have been a result of inherent differences in treatment strategies used in humans versus those used in veterinary patients with neoplastic disease.

Outcome in 202 humans with osteosarcoma that was metastatic at the time of diagnosis was recently

evaluated.<sup>2</sup> In that study, patients were treated with chemotherapy and, when possible, aggressive surgical resection of the primary tumor and metastases. Median survival time in those patients was 1.4 years. A survival advantage was observed in those in whom the primary tumor involved an extremity versus a structure in the axial portion of the skeleton, likely because of ease of surgical resection. Patients with a nonresectable macroscopic tumor burden were found to have a 5-fold increased risk of dying during the study period, compared with patients that could be rendered free of grossly apparent disease.<sup>2</sup> In that study, there was no difference in survival time between patients with metastases isolated to bone versus those with metastases to bone and lungs, and there was a decreased survival time in patients with metastases to parenchymal organs and soft tissue. In the present study, only 2 dogs had metastasis to nonpulmonary or lymph node soft tissue, so an assessment of this group of patients could not be made. In the earlier study,<sup>2</sup> a small subgroup of patients with prolonged survival times was noticed; a smaller number of metastases and the ability to render the patient free of grossly apparent disease were factors in the prolonged survival time in those patients.

It is possible that metastatic osteosarcoma that is confined to bone is a distinct clinical entity that is less aggressive than osteosarcoma that has metastasized to lung and bone. In a recent study,<sup>3</sup> palliative treatment of a subgroup of human patients with metastatic breast cancer confined to the skeleton with radiation and chemotherapy resulted in a prolonged survival time, compared with survival times associated with other forms of metastatic breast cancer. The investigators proposed that this subgroup of patients has an indolent disease course that is sensitive to standard radiation and chemotherapy protocols.

The dogs that lived the longest in our study had bone metastases with no detectable pulmonary metastases. This finding raised the question of whether the bone lesions are manifestations of metastatic or multifocal osteosarcoma. If such cases represent multifocal osteosarcoma, it is possible that surgical resection of each of the primary lesions and administration of chemotherapy would result in a survival time similar to that in dogs that receive treatment for a solitary osteosarcoma. A study<sup>4</sup> of humans with synchronous multifocal osteosarcoma revealed a strong correlation between the histologic responses of different neoplastic lesions in the same patient to neoadjuvant chemotherapy and led to the investigators' conclusion that the multiple lesions were most likely metastases from a primary bone tumor.

Resection of a primary tumor can lead to a postoperative increase in angiogenic activity and rapid growth in metastatic lesions.<sup>5,6</sup> The primary tumor releases antiangiogenic factors, and its removal at surgery may lead to a phenomenon called concomitant tumor resistance. It is possible that dogs treated with palliative radiation had longer-than-expected survival times because the primary tumor remained and suppressed the progression of metastases.

As is true for dogs with osteosarcoma and no grossly apparent metastatic lesions, treatment for metastases

after resection of the primary tumor is an essential component of management. There also appears to be some benefit to treating dogs that are receiving palliative radiation therapy with chemotherapy. In the present study, the median survival time in dogs receiving chemotherapy and palliative radiation therapy was significantly longer than in dogs that received palliative radiation therapy alone. The short-term nature of palliative radiation therapy protocols often prevents veterinary oncologists from recommending adjunctive therapy with radiation. However, our results suggest that there is a survival benefit in doing so.

Another possible explanation for the group of dogs that lived longer than expected is that stage III osteosarcoma had been incorrectly diagnosed. Recommendations for diagnosing osteosarcoma in dogs vary. However, in some dogs, diagnosis was made on the basis of signalment findings, location of lesions, and radiographic or bone scan findings, rather than histologic analysis of a bone biopsy specimen. This is standard practice at the authors' institution for diagnosis of osteosarcoma in dogs in which findings are typical of osteosarcoma. Dogs that underwent surgical excision of the primary mass had histologic confirmation of the diagnosis. However, dogs that received palliative radiation therapy alone were unlikely to have had a histologic diagnosis.

The shorter survival time observed in dogs treated with surgery alone was likely a result of the fact that 5 of the 10 dogs in that group died in the perioperative period. Those dogs did not live long enough to receive adjunctive treatment and therefore likely skewed the results toward decreased survival time in that group. Those dogs were included in the analysis because treatment was initiated for the disease and deaths were related to treatment or the disease. Although in most of those dogs it could be assumed that the owners would have authorized additional adjunctive treatment, dogs were evaluated on the basis of treatment that they received and not on the owners' intent to treat.

Four of the 5 dogs that died in the perioperative period had pulmonary metastases. Four of the 5 dogs died while anesthetized, and 1 dog died in the immediate postoperative period. A postmortem report was available for 2 dogs, both of which had pulmonary metastases. In one of those reports, it was noted that pulmonary vascular thrombosis was the most likely cause of death and that the thrombi in that dog were not typical large-vessel thromboses but rather were arterial and venous thrombi that are often associated with metastatic neoplasia. Although there were too few dogs in this series to draw conclusions about the cause of death, it is possible that dogs with pulmonary metastatic osteosarcoma are predisposed to development of pulmonary tumor emboli and sudden death during anesthesia and surgery.

Diagnosis of pulmonary metastases in the present study was made on the basis of 3-view thoracic radiographic evaluation. However, there is a possibility of misdiagnosis of metastatic disease with this technique. In 1 study,<sup>7</sup> 10 of 36 humans with osteosarcoma that received a diagnosis of pulmonary metastasis on the basis of radiographic examination

were found to have benign disease on the basis of subsequent metastectomy.

The standard of care for staging osteosarcoma in human oncology is computed tomographic imaging of the thorax.<sup>8</sup> In 1 report,<sup>9</sup> conventional radiographic imaging detected only 32% of the metastatic lesions that were observed via computed tomography. In another report,<sup>10</sup> 13% of tomographic scans revealed metastatic disease that was not detected on radiographs, although 80% of those patients in whom a diagnosis of metastatic disease was made via computed tomography, but not radiography, were eventually found to have benign disease as revealed by histologic evaluation. Computed tomography is a more sensitive imaging technique for diagnosis of thoracic metastases. However, the increased sensitivity is not necessarily beneficial to patients because of the incidence of false-positive results. In a study<sup>8</sup> in which the accuracy of computed tomography in diagnosis of pulmonary metastasis was evaluated, 51 human patients had a diagnosis of pulmonary metastatic disease on the basis of tomographic findings. All of those patients underwent pulmonary metastectomy, and of those, 57% had histologic confirmation of metastatic osteosarcoma and 43% had benign disease. Such findings underscore the difficulty in accurately staging osteosarcoma and metastatic disease in dogs.

Some limitations exist in regard to findings of the present study because of its retrospective design and absence of any standardization of treatment groups. The decision to treat stage III osteosarcoma is uncommon, and because of this, treatment was often tailored to the metastatic sites involved and to owner and clinician preferences. A prospective study with standardized treatment groups would be needed to verify our findings. Another limitation was that survival time was often owner dependent because in most instances, owners elected to euthanize their dogs when the quality of life was determined to be poor, rather than permitting dogs to die from the disease. Because dogs with bone metastases are more likely to have signs of pain and dogs with advanced pulmonary metastases are more likely to have signs of systemic illness, it is possible that dogs with bone metastases lived longer because owners failed to determine the level of pain or

quality of life adequately or that the effects of bone metastases can be palliated more effectively than soft tissue metastases.

Treatment of dogs with stage III osteosarcoma can result in various survival times. The disease is associated with a guarded prognosis and has a median survival time of 76 days. Some dogs may survive much longer than that (the range of survival times among dogs in this study was 0 to 1,583 days), but it is difficult to identify those dogs prior to the initiation of treatment. Dogs with bone metastases and those that were treated with palliative radiation therapy and chemotherapy had the longest survival times.

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a. SPSS, version 11.0, SPSS Inc, Chicago, Ill.

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