Abstract. Radiotherapy is effective for the palliation of pain associated with primary and metastatic bony neoplasia in dogs and humans, but no standard treatment protocol has been established. The goal of this study was to evaluate a 3 x 8 Gy and a 4 x 6 Gy protocol using electrons with a betatron or linear accelerator for the treatment of appendicular osteosarcoma in 54 dogs. Thirty-three dogs received chemotherapy consisting of carboplatin IV concurrently with radiotherapy. Eighty-three % (n=45) of the dogs experienced pain relief during or following treatment. The median duration of pain relief from treatment start was 53 days. In conclusion, both protocols are effective for palliation of clinical signs of canine appendicular osteosarcoma. The outcome reported here is similar to the results of other studies using Co photons. The use of chemotherapy did not improve the response to radiotherapy.

Palliative treatment for dogs with appendicular osteosarcoma consists of radiotherapy with or without chemotherapy. At this time, there is no standard palliative protocol for canine appendicular osteosarcoma and little is known about the effect of different forms of radiation, as well as patient and tumour characteristics that affect treatment outcome. In human medicine, it has been well established that radiation therapy is an effective modality for palliative treatment of primary bone tumours and bone metastasis, but optimal dose-response data have not been defined and fractionation schemes remain controversial (1-6). Although, in contrast to primary osteosarcoma in dogs, bony metastases in humans are mainly of epithelial origin, including breast, prostate, lung, thyroid and kidney, the pathophysiological mechanisms of malignant bone pain are similar and are not correlated to tumour type, location or size (7). The release of cytokines mediate osteoclastic bone destruction and modulate pain perception by stimulating nociceptors located in the periosteum. Increased pressure within the bone, mechanical stress of the weakened bone, microfractures, the stretching of the periosteum, reactive muscle spasm or nerve root infiltration are other possible mechanisms of malignant bone pain (8-10). Administration of radiation results in a cytotoxic process affecting normal bone cells that release chemical mediators (prostaglandins, notably PGE2) in response to the neoplastic process. Later onset pain relief is related to recalcification and repair of osteolytic lesions (11).

Numerous approaches to palliative radiotherapy protocols for the treatment of canine osteosarcoma have been described using cobalt radiation (12-16). Overall response rates in these studies ranged from 74% (14) to 92% (15), with median duration of response intervals ranging from 73 days (14) to 130 days (12) and median survival ranging widely from 122 days (14) to 313 days (15).

At our institution, high energy electron radiotherapy has been used. Therefore, the purpose of this retrospective study was to: i) evaluate the effectiveness of this type of radiation, ii) compare the results to responses to other palliative protocols, and iii) identify prognostic factors that may influence tumour response and survival.

Materials and Methods

Subject selection. The radiotherapy database of the section of diagnostic imaging and radiation oncology, Vetsuisse Faculty, University of Zürich, Switzerland, was searched for records of all dogs that had received palliative radiation therapy for the treatment of appendicular osteosarcoma. This search revealed 72 dogs which had received radiation therapy between 1996 and 2003. Of these dogs, 18 were excluded from this study due to the lack of adequate follow-up information in the record.
Data collection. The medical records of 54 dogs were reviewed to obtain information regarding symptoms, duration of lameness prior to treatment, clinical presentation, ALP plasma levels prior to therapy, which of two palliative radiation protocols was used and whether this was with or without concurrent chemotherapy. The onset of response to treatment after irradiation, duration of response, toxicity associated with the treatment, presence of metastases, overall survival and cause of death were also examined. Radiographs of good quality were available for 34 dogs and reviewed by one of the authors (D. Nitzl). Twenty-eight dogs had cytological or histological confirmation of osteosarcoma and 26 were treated based on a presumptive diagnosis determined by typical radiographic findings.

Attempts were made to obtain accurate follow-up information for subjects not returned for re-examination by telephoning the owners and through detailed questionnaires.

Treatment protocol. Radiotherapy consisted of 24 Gy given either in 4 fractions of 6 Gy on days 0, 7, 14 and 21 to 18 dogs, or 3 fractions of 8 Gy given on days 0, 7 and 21 to 36 dogs. All dogs received radiotherapy using a betatron (BBC, Baden, Switzerland) or a linear accelerator (ABB Varian, Baden, Switzerland). A 3-cm margin beyond gross tumour and radiographically apparent bone involvement was irradiated in a single field. Whenever possible, a strip of skin was spared to avoid lymphedema. Treatment planning was done manually.

In 33 dogs, systemic chemotherapy was given concurrently with radiotherapy starting on day 0. Carboplatin (EBewe Pharma GmbH) was administered within 2 hours either before or after radiotherapy at 250 mg/m², intravenously for 2 to 4 treatments q 3 weeks. Most dogs in this study received non-steroidal anti-inflammatory drugs before, during and/or after radiation treatment.

Statistical evaluation. The duration of clinical signs was calculated from the day of onset of lameness to the day of evaluation at our clinic. Lameness was graded according to a scale from 0-5, with grade 0 being defined as "no lameness" and grade 5 as "non-weight-bearing".

Response was evaluated by the owner and the clinicians and defined as an improvement of the degree of lameness. Response was defined as "complete" if the lameness had resolved (L0), and "partial" if the dog continued to be lame, but to a lesser degree. No response to treatment was defined as a lack of clinical improvement or a worsening of clinical signs.

Time to onset of response was defined as from the first day of radiotherapy to the day of first reported response. Duration of response was defined as from the day of onset of response to the first day of recurrence or worsening of lameness. Time to relapse was calculated from the first day of radiotherapy to the first day of recurrence or worsening of lameness. Survival time was measured from the first day of radiotherapy to the date of death or euthanasia.

Toxicity induced by radiotherapy was evaluated at each visit and graded according to the RTOG chart (17). Toxicity induced by chemotherapy was evaluated at each visit by a physical examination and a complete blood count (CBC) 7-10 days after chemotherapy.

First, descriptive statistics of the variables in the data set were computed (counts and relative frequencies for discrete ones and means and standard deviations (medians and ranges) for continuous ones). Secondly, survival analysis was computed by applying Kaplan-Meier statistics together with the log rank test or, where necessary, the Breslow-Gehan-Wilcoxon test for discrete predictors. Alternatively, Cox regression analysis was applied for continuous predictors such as age. Significance was assigned to values of p<0.05.

Results

Subjects. The population in this study consisted of 20 male and 34 female dogs. The median age was 8.5 years (range 2 to 14). The median body weight was 40 kg (range 10 to 71). The most commonly represented breeds included the Rottweiler (n=7), Bernese Mountain Dog (n=6), Great Dane (n=4), German Shepherd (n=4) and Leonberger (n=3).

All dogs included in this study presented with lameness and swelling of the affected limb. The median duration of clinical signs prior to radiation was 35 days (range 3 to 214). For 38 dogs, a grade of lameness could be assigned. Twenty-three dogs (60%) were still weight-bearing, while 15 dogs (40%) were intermittently or constantly non-weight-bearing at the time of diagnosis of osteosarcoma.

The most common sites of primary tumour involvement included distal radius (n=19), distal tibia (n=13, one of these dogs showed involvement of the distal fibula as well), and proximal humerus (n=12). For 52 dogs, ALP levels were recorded, of which 18 dogs had an increased plasma level of ALP (ALP > 98 U/l) on bloodwork performed prior to radiation therapy.

None of these variables evaluated had a statistically significant influence on the treatment outcome.

Radiographic evaluation. Radiographs of the tumour site were available for 34 dogs. The percentage of bone involvement estimated from radiographs ranged from 16 to 100% (median 38%). For the purpose of comparing the results of our study with previous reports (Ramirez, Green), the ratio of bone involvement was divided into two groups: the first group included dogs with 41% bone involvement and more (n=15), while the second group had less than 41% bone involvement (n=19). With regard to response, duration of response and survival, there was no statistically significant difference between these two groups. None of the other radiographic descriptors evaluated in our study were related to treatment outcome.

Response to treatment. Overall, 83% of the dogs (n=45) treated with radiation therapy experienced pain relief during or following treatment. For 38 dogs, the degree of pain relief was noted in the record. 36.8% of these dogs (n=14) experienced complete pain relief. In 63.2% of the dogs (n=24), partial pain relief was achieved.

For 40 dogs, the day of onset of response was noted in the records. Twenty-five % showed clinical improvement by day 7 after treatment start, 50% by day 14 and 75% of the dogs experienced improvement in limb function by day 21.
The onset of response ranged from 1 to 34 days. The median onset of response for dogs that were weight-bearing was 21 days compared to a median of 7 days for the dogs that were non-weight-bearing prior to therapy. The duration of response was noted in the records of 36 dogs, ranging from 6 to 482 days (median 53 days).

Eleven dogs (20%) experienced mild to moderate signs of acute radiation side-effects like swelling, changes in pigmentation and/or alopecia (ROTG Grade 1). The chemotherapy treatment was generally well-tolerated and none of the dogs had to be hospitalised or receive treatment due to adverse side-effects.

With regard to response and duration of response, there was no statistically significant difference by Kaplan-Meier analysis and log rank test between the group of dogs that received chemotherapy and the group that did not (p=0.55 and p=0.27, respectively), and there was no difference between the two radiation protocols (4 fractions of 6 Gy versus 3 fractions of 8 Gy).

**Survival.** The 33 dogs that received chemotherapy in combination with radiation treatment had a median survival of 120 days compared to a median survival of 90 days for dogs that did not receive chemotherapy. However, there was no statistical difference between these two groups (p=0.1331).

The median survival for dogs with ALP levels in the normal range was 98 days compared to a median survival of 70 days for dogs with elevated ALP levels. No statistical difference was found between these groups (p=0.1842).

The overall identified metastatic rate for this population was 33%. Eight dogs (15%) had signs of pulmonary metastatic disease on thoracic radiographs prior to therapy, of which a local response at the primary tumour site was achieved in 6 dogs. The median survival for these 6 dogs was 90 days. In 10 dogs (18%), development of metastasis during or after therapy was detected. The median survival for these dogs was 150 days. Interestingly, 9 of these 10 dogs had received chemotherapy concurrently with radiation treatment.

Twenty-six dogs were euthanized due to local disease, 6 of which had not responded to radiation treatment. Fourteen dogs were euthanized or died of metastatic disease. Seven dogs died of tumour-unrelated causes, while for 7 dogs the cause of death was not known.

**Discussion**

The goal of palliative radiotherapy in dogs with appendicular osteosarcoma is to alleviate pain and improve limb function. Both protocols used in the present study fulfilled the requirements of a palliative treatment. They were well tolerated and were not associated with acute effects that reduced the animals' quality of life. It allowed for the dogs to be treated as outpatients. Acute radiation reactions were low-grade and limited to the skin, which is consistent with recent reports (12-16). In this study, palliative radiotherapy resulted in pain relief and improvement of limb function in 45 out of 54 dogs (83%), with over a third (36%) of the dogs that responded to treatment experiencing complete pain relief. The onset of response was generally noted rapidly, with a median of 14 days after treatment start. The duration of response varied widely, ranging from 6 to 482 days (median 53 days).

Differences in the recruited subject population, as well as the variety of treatment techniques, schedules, subject and tumour characteristics and small sample sizes make it difficult to directly compare the outcome of our study to those of prior reports, and discrepancies in response rates, duration of response and survival might be due to artefacts. The observed treatment response is influenced by the type of pain scale used and "complete response" and "partial response" cannot be directly compared. In addition to defining response, there is an inherent difficulty in measuring a response to radiotherapy given as a local treatment when pain is often also palliated by other systemic agents, including a variety of analgesics and chemotherapy. In the present study, almost all dogs received systemic analgesics (mainly non-steroidal anti-inflammatory drugs) before, concurrently and/or after radiation therapy.

Since traditional end-points, such as survival or tumour control, are not appropriate measurements of quality of life, it is important to concentrate on end-points such as response rate and duration of response when comparing the effectiveness of different treatment protocols for palliation of pain associated with osteosarcoma.

Comparing the different studies in veterinary subjects (12-16), no protocol for palliative radiation treatment for dogs with osteosarcoma is superior and, according to our results, irradiation with electrons does not seem to offer any advantage over other forms of radiotherapy. Therefore, a standard treatment regimen has not yet been determined.

The population characteristics in our study were similar to those of previous reports (12-16). No variables in the present study were found to be significant with regard to response, duration of response or survival. In previous studies, the duration of response was significantly improved when less than 50% of the bone was involved, when the lesions were nonlytic on radiographs and with osteosarcoma in the proximal humerus (14, 15). This was not confirmed in our study.

The results of a study on palliative radiotherapy of appendicular osteosarcoma in 95 dogs suggests that chemotherapy with carboplatin or carboplatin plus cisplatin in combination with radiation therapy improves the probability of response and also appears to be related to
longer response duration (14). This was not confirmed by our study or in other reports (15, 16). Thus, chemotherapy might not be indicated in cases that receive palliative radiotherapy for appendicular osteosarcoma, although the palliative benefit of chemotherapy is difficult to measure. Patients may experience pain relief without showing objective tumour response. In the present study, chemotherapy was given for two purposes: i) to increase cell killing at the primary tumour site with the hope of prolonging the duration of pain-free response, and ii) to delay development of distant metastasis. In the present study, there was no significant difference in response rate, duration of response or survival for dogs that received radiation therapy in combination with or without chemotherapy. Platinum drugs are thought to be radiosensitizers when given within an hour of radiation (18). In the present study, attempts were made to coordinate the administration of chemotherapy within two hours prior to radiation treatment, but no enhancement of local radiotherapy effects in dogs was noticed and chemotherapy did not seem to delay the development of distant metastasis. Nine of the 10 dogs that received pulmonary metastasis during or after therapy had received chemotherapy concurrently with radiation therapy.

In one study, 15 dogs with appendicular osteosarcoma were treated with a radiation therapy protocol that eliminated the two-week gap in the three-fraction palliative protocol (3 x 10 Gy on days 0, 7, 21) by administering 4 x 8 Gy-fractions on days 0, 7, 14 and 21 (15). The response rate in that study was high (92%) and the median survival of 315 days was over four times longer than in a previous report (14). In the present study, there was no statistically significant difference for the dogs that received 3 x 8 Gy versus dogs that received 4 x 6 Gy with regard to response (p=0.42), duration of response (p=0.44) or survival (p=0.87).

Our study design had several limitations. As the study was retrospective, we were unable to collect all data by reviewing the records or talking to the owners. This led to the exclusion of many subjects that might otherwise have been included. For this reason, the sample size was small and might not represent the actual population distribution. Additionally, for only about half of the dogs was a histopathological/cytological confirmation of the diagnosis obtained; the other half were treated based on a presumptive diagnosis by typical radiographic findings. It is possible that not all of the tumours were osteosarcomas.

In conclusion, both our palliative radiation protocols were effective for palliation of pain associated with canine appendicular osteosarcoma. The outcome reported here is similar to the results of other studies using Co photons. The use of chemotherapy did not improve the response to radiotherapy and did not seem to delay the development of distant metastasis.

References


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