Effect of single dose radiation therapy on weight-bearing lameness in dogs with elbow osteoarthritis

Amy S. Kapatkin[1]; Barbro Nordquist[2]; Tanya C. Garcia[3]; Maureen A. Griffin[4]; Alain Theon[1]; Sun Kim[5]; Kei Hayashi[6]

[1]Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, CA, USA; [2]Evidensia Strömsholm Specialty Hospital, Strömsholm, Sweden; [3]Department of Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California, Davis, CA, USA; [4]School of Veterinary Medicine, University of California, Davis, CA, USA; [5] Veterinary Medical Center, East Lansing, MI, USA; [6] Cornell University, College of Veterinary Medicine, Ithaca, NY, USA

Keywords

Elbow, osteoarthritis, radiotherapy, force platform gait analysis

Summary

Objectives: To determine if a single low dose of radiation therapy in dogs with osteoarthritis of the elbow joint was associated with a detectable improvement in their lameness and pain as documented by force platform gait analysis.

Methods: In this cohort longitudinal observational study, five Labrador Retrievers with lameness due to elbow osteoarthritis that was unresponsive to medical treatment were removed from all non-steroidal anti-inflammatory and analgesic medications. A single treatment of radiation therapy delivering 10 Gray was performed on the affected elbow joint(s). Force platform gait analysis was used to assess the ground reaction forces of a limb affected with elbow osteoarthritis both before and after radiation therapy.

Results: Significant differences occurred in the weight-bearing on an affected limb with elbow osteoarthritis after radiation therapy at weeks six and 14. Change due to treatment was particularly apparent in dogs with unilateral elbow osteoarthritis.

Clinical significance: Administering a single low dose of radiation therapy may have a short-term benefit in dogs with elbow osteoarthritis, which is similar to the evidence supporting the use of radiation therapy in horses with orthopaedic disease.

Correspondence to:
Dr. Amy Kapatkin
University of California-Davis
Surgical & Radiological Sciences
2112 Tupper Hall
Davis, California 95616
United States
Phone: +1 530 752 6787
Fax: +1 530 752 6042
Email: askapatkin@ucdavis.edu

Vet Comp Orthop Traumatol 2016; 29: 338–343
http://dx.doi.org/10.3415/VCOT-15-11-0183
Received: November 11, 2015
Accepted: April 11, 2016
Epub ahead of print: June 1, 2016

Introduction

Chronic elbow osteoarthritis is the sequela from a variety of heritable elbow conditions of young dogs. Albeit a common cause for lameness in the dog, treatment for canine elbow osteoarthritis is largely palliative. Current treatments mainly focus on medical management (analgesics, non-steroidal anti-inflammatory drugs, nutraceuticals, weight control, physical rehabilitation, and activity modifications) or surgical techniques that transfer the load bearing in the elbow joint or salvage the joint (1). The use of other interventions such as electrostimulated acupuncture showed no beneficial effect on elbow osteoarthritis (2). Administration of platelet rich plasma and stem cells to dogs with chronic osteoarthritis showed some kinetic gait improvements in preliminary clinical trials, but larger clinical studies are needed to fully evaluate their effects on dogs with chronic elbow osteoarthritis (1, 3–7).

Low dose radiation therapy has been used clinically to treat a variety of degenerative inflammatory disorders in humans. The treatment of painful orthopaedic disorders with radiotherapy is not well understood (8). However, low dose radiation therapy has direct anti-inflammatory effects on articular tissues, thereby leading to a decrease in bone loss, synovial proliferation, and signs of pain, and furthermore it reduces nitrous oxide production within the joint (8–11). Clinical outcome is dependent on the underlying disease process; one meta-analysis showed a mean clinical improvement in 56% of human patients with osteoarthritis, and patients with mild to moderate radiographic changes had better results (11). A more recent study reported improvement in quality of life in 59% of humans suffering from more severe degenerative joint diseases including osteoarthritis, and extensive joint destruction was associated with a worse prognosis (12).

Low dose radiotherapy is reported to be effective in improving lameness of horses that suffer from various degenerative orthopaedic problems and returning them to the racetrack (8, 13). A success rate of

60–70% has been reported for radiotherapy treatment (with doses ranging between 5 and 15 Gray [Gy]) of painful orthopaedic disorders in horses that were refractory to other treatments (8). A reported benefit of low dose radiation is that it allows for normal bone healing while inhibiting excessive proliferation of new bone, which may be of value in osteoarthritic conditions (8). In rats, low dose radiotherapy has been experimentally shown to prevent the progression of adjuvant arthritis (14–15). According to one study, low dose radiotherapy in rats was associated with a reduction in cartilage and bone destruction in relation to alteration of inducible nitric oxide synthase activity (15).

Due to the reported beneficial effect of radiotherapy on human and equine osteoarthritis, the purpose of this trial was to determine if dogs with osteoarthritis of the elbow joint treated with a single low dose of radiation therapy had a detectable improvement in their lameness and pain documented by force platform gait analysis. Our null hypothesis was that dogs treated with radiotherapy would not demonstrate any difference in their kinetic gait parameters over time.

Materials and methods

The study was designed as a cohort longitudinal observational study. Six dogs were enrolled in the study. Criteria for enrollment were as follows: the dogs had a diagnosis of elbow osteoarthritis that was treated medically for at least six months and were lame in at least one thoracic limb due to elbow pain despite medical management; the dogs were Labrador Retrievers eight years or older with a body condition score of 5 to 7 out of 9. Owner consent was obtained for all dogs enrolled and the study was approved by the Institutional Animal Care and Use Committee at the University of California-Davis. Physical examination, orthopaedic examination, haematology, biochemical analysis, urinalysis, and elbow radiography were performed prior to enrollment into the study. Dogs were removed from all treatment with nonsteroidal anti-inflammatory drugs and analgesics at one week prior to the first gait analysis. Glucosamine and other supplements were allowed.

After screening, force platform gait analysis was performed weekly for the first three weeks (prior to radiation therapy) to acclimate the dogs to the force platform. The ground reaction forces from these weeks were all averaged for each dog and considered to be the control data for each dog.

Dogs were trotted over two 60 × 40 cm Kistler force platforms[a] in series by one of three trained investigators and the ground reaction force data were collected with standard software[b]. Dogs performed five valid trials per session. Trials were considered valid when the ipsilateral thoracic limb and pelvic limb completely struck the force platform and all four limbs were recorded at the same gait cycle on the two platforms in series. The dog's velocity was constrained to a small range (1.6 and 1.9 m/s), and the dog's acceleration was ± 0.5 m/s^2 (measured with five photoelectric cells) (16–18).

Peak vertical force (PVF) and vertical impulse (VI) were determined for all limbs of each dog at each time point. The asymmetry index for PVF of the thoracic limbs was calculated [(worse/affected limb – contralateral)/(average of both limbs) ×100] for each dog.

On the day of the third gait analysis of the baseline gait data, the dogs were anaesthetized following the force plate gait session and a single treatment of radiation therapy delivering 10 Gy was performed using a 4-MV linear accelerator[c] on the affected elbow joint(s). The elbow joint was defined as affected if the dog had visible signs of lameness on the limb. All dogs had some elbow joint osteoarthritis, yet only those dogs that had assymetry indexes less than 30 were classified as being bilaterally affected and had both elbows receive the radiation treatment. At the time of discharge, the owner of each dog was provided with tramadol (approximately 2.2 mg/kg PO twice daily for three days) for the treatment of any potential pain following the radiation treatment. The dogs returned for a session of force plate gait analysis at two and four weeks following the radiation treatment. Theareafter, force platform gait analysis was performed monthly for one year or until the dog failed the trial. Trial failure occurred when the owner considered that their dog required analgesic medication for pain management.

a Kistler Instrument Corp, Amherst, NY, USA
b Acquire 7.33V: Sharon Software, Dewitt, MI, USA
c Clinac 4: Varian corporation, Palo Alto, CA, USA

Statistical analysis

Kinetic values were assessed using a mixed model analysis of variance[d] that accounted for repeated trials within dogs. The effects of trial number, week number, dog speed, and limb condition (the worse limb was called 'affected'; the untreated or treated but less affected limb was called 'contralateral') and interactions between trial and limb condition were included in the model because they were significant in a Type 3 test of fixed effects ($p < 0.05$). Normality of the responses was confirmed by assessing the distribution of the residuals using the Shapiro-Wilks test. Pairwise comparisons were made between pre-treatment (week 0) and each of the following gait sessions post-treatment (2 weeks, 4 weeks, and then monthly for the remainder of the study with time intervals of 4 weeks ± 1 week). Differences in least-squared means with p-values <0.05 were considered statistically significant. Summary data are reported as least squared means and standard error. Three separate statistical analyses were performed: 1) with all dogs, only considering the worse limb in bilateral dogs and the affected limb unilateral dogs as the *affected* limb, 2) including both affected limbs in the bilateral dogs and the affected limb in unilateral dogs as *affected*, 3) including only the two dogs that were unilaterally affected.

Results

Six dogs met all inclusion criteria and were enrolled in the study. One dog dropped out after the first study date and no data were

d SAS 9.3: SAS Institute, Cary, NC, USA

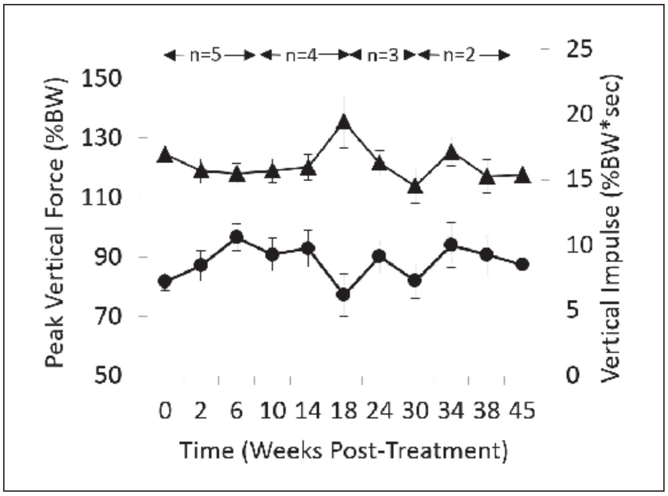

Figure 1 Peak vertical force (circles) and vertical impulse (triangles) least-squared mean and standard error for all dogs including only one limb, the most affected limb, at each time point. The number of subjects for the specified time range is listed (n = subject number).

used from this dog. Three of the five dogs were clinically affected by their elbow dysplasia bilaterally and two dogs were only clinical in one elbow as demonstrated by visible lameness of the identified limbs and with signs of pain on manipulation of the elbows. The bilateral clinically affected dogs had asymmetry indexes that were 25.9, 4.5 and 7.2, indicating minimal difference between the two thoracic limbs. The assymmetry indexes of the dogs that were unilaterally lame were 62.3 and 64, indicating a large difference in the use of their thoracic limbs. Therefore, three dogs received radiotherapy on both elbows, one dog received radiotherapy on the left elbow, and the other dog on the right elbow.

Two of the dogs with bilateral elbow dysplasia completed the one year trial without needing any anti-inflammatory or analgesic drugs. One of these two dogs was euthanatized three months after the end of the study because it developed hyperadrenocorticism and other lameness problems. The other dog that completed the study was euthanatized two years after the end of the study for an undiagnosed cervical myelopathy at 13 years of age. Two dogs dropped out of the study because the owners believed that their dog needed nonsteroidal drugs treatment for hip osteoarthritis. One was treated bilaterally and quit the study at three months post-treatment, and the other dog had only the left elbow treated but dropped out of the study at five months post-treatment. The remaining dog with right elbow pain dropped out of the study at six months because it started showing signs of pain after hunting and needed nonsteroidal medications. In summary, the statistical comparisons of response to treatment were performed on five dogs up to three months, four dogs to five months, three dogs to six months, and two dogs for 12 months.

When comparing only the worse limb from each dog, no significant differences occurred in the PVF or VI at each time point compared to pre-treatment, except for week six which showed an increase of 15 ± 4.6% bodyweight (BW) in PVF (least squared mean ± mean standard error) (▶Figure 1). When analyzing all affected limbs of all dogs, PVF was not significantly different before and after radiation therapy except for week six which showed an increase of 10 ± 3.6%BW in PVF and at week 10 which showed an increase of 8 ± 4.6%BW ($p = 0.056$) (▶Figure 2). When analyzing all affected limbs of all dogs, VI was not significantly different before and after radiation therapy except for week 14 which showed an increase of 0.62 ± 0.41%BW × sec.

For the two unilaterally affected dogs, there was a significant increase of PVF in the affected thoracic limbs at weeks six, 10, 14 and 24 ($p < 0.05$) (▶Figure 3). There was also significant increases in the contralateral limbs at all timepoints. There were no significant differences in VI of the affected limbs at any timepoint, but there was a significant decrease at weeks two through 24 compared to pre-treatment. For the bilaterally affected dogs, there was a significant decrease in the asymmetry index at week 14 (▶Figure 4), but not at other time points. For the unilaterally affected dogs, the asymmetry index significantly decreased at all time points compared to pre-treatment, except for week 30 at which time there was only data available from one dog. The PVF of each limb of each individual dog is shown in ▶Figure 5.

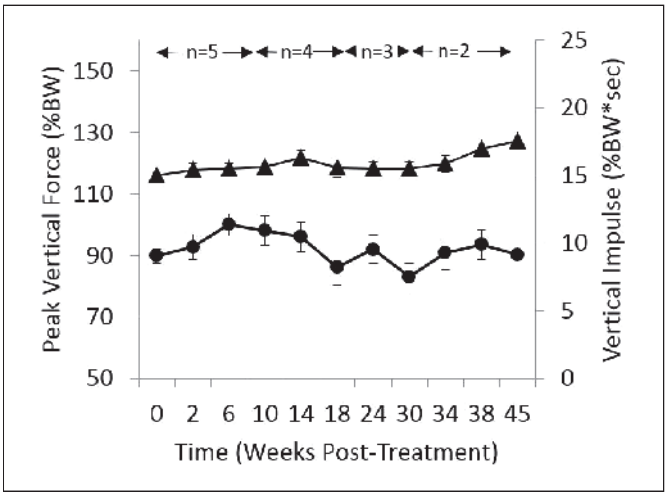

Figure 2 Peak vertical force (circles) and vertical impulse (triangles) least-squared mean and standard error for all dogs including both affected and treated limbs at each time point. The number of subjects for the specified time range is listed (n = subject number).

Discussion

The null hypothesis was rejected. There were some significant differences in weight-bearing on the affected limb with elbow osteoarthritis after radiation therapy, which were especially apparent at six to 14 weeks. Change due to treatment was particularly apparent in dogs with unilateral elbow osteoarthritis where increases of PVF increased at most time points after treatment. At early time points following radiation therapy for all dogs when considering both the most affected limb of each dog and all affected limbs, there was increased weight bearing on the treated limb and a slight decrease in VI. In the two dogs with unilateral osteoarthritis, PVF increased at all time points post-treatment in the affected and the contralateral limb. Therefore, administering a single low dose of radiation therapy may have had a short-term benefit in dogs with elbow osteoarthritis, which is similar to the evidence supporting the use of radiation therapy in horses with orthopaedic disease (8).

Kinetic gait analysis is an excellent objective tool for clinical studies to document improvement of lameness after treatment. Yet statistical improvement of gait parameters does not always translate to significant clinical improvements in the dog's gait. In general, at least a 10% improvement on the force platform values is needed to notice any clinical difference. This was seen at some time points and therefore we concluded there were some short- term improvements in the use of their affected thoracic limbs. A 20% improvement would be even more convincing because that amount of improvement would also eliminate the approximately 4.5% variation documented in VI during inter-week data collection (19).

The asymmetry index data showed that dogs that were clinically affected unilaterally from elbow osteoarthritis were dramatically asymmetric in their thoracic limbs, whereas dogs that were clinically affected bilaterally were mildly asymmetric in their thoracic limbs. This makes sense because although dogs with clinical bilateral elbow osteoarthritis are lame, they may be equally lame in both limbs and therefore appear to be symmetrical despite the fact they have abnormal PVF and VI data. These asymmetry results agreed with the clinical assessment of lameness as unilateral or bilateral.

In one unilateral dog (dog B), there was in increase in PVF post-treatment in both the treated and contralateral limb. This could mean there was an effect of treat-

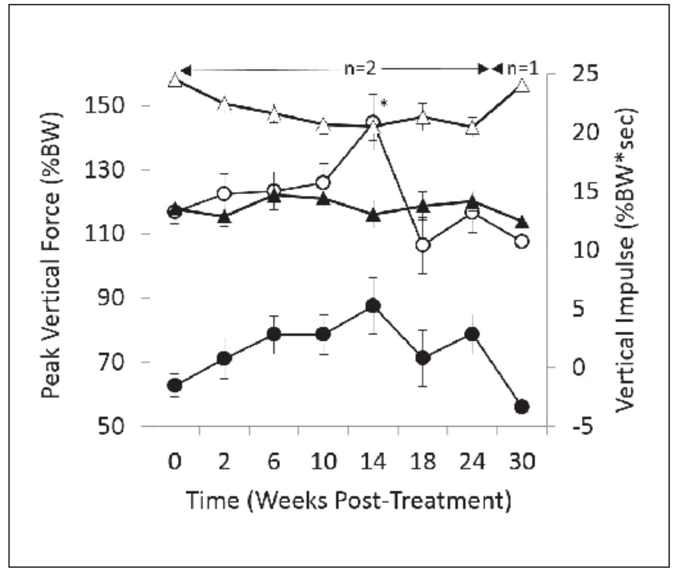

Figure 3 Peak vertical force (circles) and vertical impulse (triangles) least-squared mean and standard error for only the two dogs with unilateral osteoarthritis at each time point. Affected/treated limbs are shown with solid markers; contralateral limbs are shown with open markers. The number of subjects for the specified time range is listed (n = subject number). *Indicates there was only one dog's data for this time point.

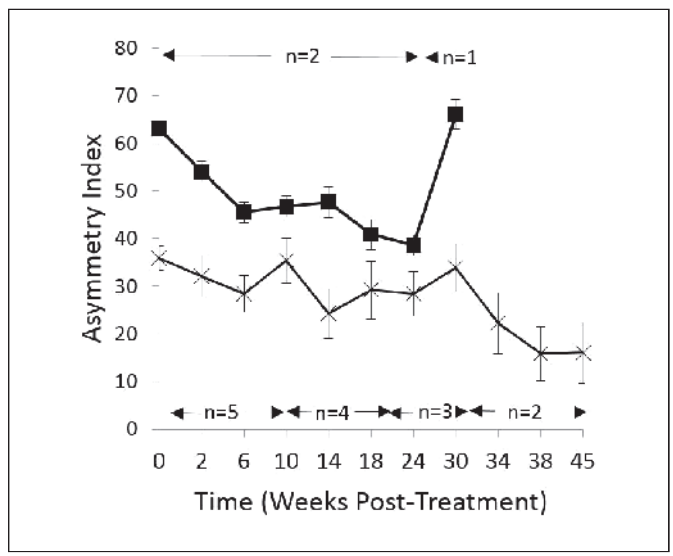

Figure 4 Asymmetry index of peak vertical force least-square means and standard error at each time point for all dogs. Dogs with unilateral osteoarthritis are shown with filled square markers and dogs with bilateral osteoarthritis are shown with X markers. Top row shows n = subject numbers for unilateral dogs, bottom row shows n = subject number for bilateral dogs.

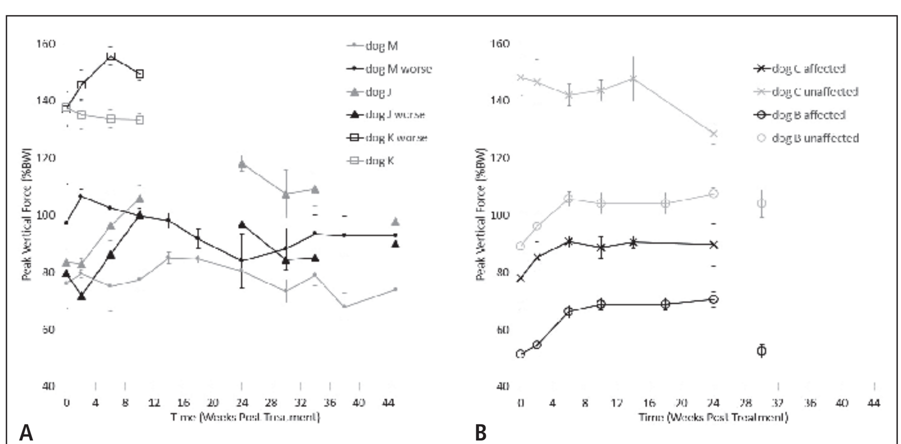

Figure 5 Peak vertical force for the **(A)** three dogs with bilaterally affected/treated limbs and **(B)** two dogs with unilaterally affected/treated limbs.

ment and the dog was comfortable shifting more weight from pelvic to thoracic. In the second unilateral dog (dog C), there was in increase in PVF in the treated limb and corresponding steady or decreasing PVF in the contralateral limb. This is more reflective of what would be seen if the dog was more comfortable on the treated limb so it bore more weight on that limb and less on the contralateral.

The finding of owner's perception of improvement corresponded with the slight improvement (increase in weight bearing) evident from PVF data. The owner's perception of improvement even at the later time points, which did not show a change in PVF, could be a placebo effect. Dogs receiving attention during a treatment protocol may have an endorphin release that could be interpreted by the owners as an improvement from the treatment. Another chronic elbow osteoarthritis study showed similar owner perceptions of recovery with no force platform improvements (2).

Though this study has value in demonstrating a short-term or potential clinical benefit due to single low dose radiotherapy in dogs with elbow osteoarthritis, it has limitations. Most notably is the small sample size. We chose to use only Labrador Retrievers to try to eliminate breed differences in gait, and therefore these data cannot be extrapolated to other breeds of dogs. Furthermore, the dogs in this study were only evaluated and treated for their clinically affected limbs. Due to the nature of elbow dysplasia and osteoarthritis, the unilaterally affected dogs had mild disease in the contralateral limb that was undetectable by clinical measures, and this may have influenced the results. Other joints besides the elbows were not radiographed in these dogs unless they were clinically affected. No dog had additional signs of pain or changes in any thoracic limb joint other than the elbow. Three dogs had to be removed from the study due to perceived pain by their owners and requiring nonsteroidal anti-inflammatory medication. Up to the point they dropped out, there was no detectable improvement in their weight-bearing.

Elbow osteoarthritis is often advanced in older dogs leading to a decreased range of motion of the elbow joint and abnormal kinematics of the elbow joint. Although low dose radiotherapy is reported to potentially reduce the production of new bone leading to more advanced disease and signs of pain, the dogs in this study were middle aged with advanced disease that may not have benefited the same as a dog with early elbow disease. It is possible that low dose radiotherapy used at the onset of lameness would have both a more pronounced effect and longer effect than that observed in the dogs in this study.

Finally, as this type of treatment has not previously been evaluated in dogs, the therapeutic radiotherapy dose is unknown. It is possible that a different radiotherapy protocol, including multiple treatments, higher doses, or both may have more beneficial effects in dogs with elbow osteoarthritis. Clinical studies in horses and humans have established appropriate radiation doses that are therapeutic while minimizing any side effects, and the radiation dose elected for this study was extrapolated from previous research in horses and humans (8, 20–21). It is important to consider that ionizing radiation has potential risks for long-term side effects at high doses or multiple treatments. The use of a low dose of radiation is desirable because it greatly diminishes the risk of induction of neoplasia. One human study with a four year follow-up period reported that there was not any development of secondary malignancies, and literature searches did not reveal any publications related to radiotherapy-induced malignancy secondary to the use of low dose radiotherapy for degenerative joint diseases (21).

In conclusion, the use of 10 Gy as a single dose of radiotherapy for elbow osteoarthritis may have a small, short lived beneficial effect in dogs. Other radiotherapy protocols may have different results.

Acknowledgements

This study was supported with a grant from the Center for Companion Animal Health, School of Veterinary Medicine, University of California, Davis and VMTH Resident Research Grant

Conflict of interest

The authors have no conflicts of interest, financial or otherwise, to report.

References

1. Coppieters E, Gielen I, Verhoeven G, et al. Erosion of the medial compartment of the canine elbow: occurrence, diagnosis and currently available treatment options. Vet Comp Orthop Traumatol 2015; 28: 9–18.
2. Kapatkin AS, Tomasic M, Beech J, et al. Effects of electrostimulated acupuncture on ground reaction forces and pain scores in dogs with chronic elbow joint arthritis. J Am Vet Med Assoc 2006; 228: 1350-1354.
3. Franklin S, Cook J. Prospective trial of autologous conditioned plasma versus hyaluronan plus corticosteroid for elbow osteoarthritis in dogs. Can Vet J 2013; 54: 881–884.
4. Fahie M, Ortolano G, Guercio V, et al. A randomized controlled trial of the efficacy of autologous platelet therapy for the treatment of osteoarthritis in dogs. J Am Vet Med Assoc 2013; 243: 1291-1297.
5. Sun Y, Feng Y, Zhang C, et al. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. Int Orthop 2010; 34: 589–597.
6. Vilar J, Morales M, Santana A, et al. Controlled, blinded force platform analysis of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells associated to PRGF-Endoret in osteoarthritic dogs. BMC Vet Res 2013; 9: 131.
7. Guercio A, Di Marco P, Casella S, et al. Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. Cell Biol Int 2012; 36: 189-194.
8. Theon A. Radiation therapy. In: Ross MW, Dyson SJ. Diagnosis and Management of Lameness in the Horse. 2nd ed. St. Louis, Missouri: Elsevier Saunders; 2003. pg. 783–787.
9. Raekallio MR, Hielm-Bjorkman AK, Kehonen J, et al. Evaluation of adverse effects of long-term orally administered carprofen in dogs. J Am Vet Assoc 2006; 228: 876–880.
10. Roedel F, Kley N, Beuscher HU, et al. Anti-inflammatory effect of low-dose X-irradiationand the involvement of a TGF-β_1-induced down-regulation of leukocyte/endothelial cell adhesion. Int J Radiat Biol 2002; 78: 711–719.
11. Kresnik E, Mikosch P, Gallowitsch HJ, et al. Clinical outcome of radiosynoviorthesis; a meta-analysis including 2190 treated joints. Nucl Med Commun 2002; 23: 683–688.
12. Rau H, Franke C, Goretzki G, et al. Radiosynoviorthesis in osteoarthritis and other disorders with concomitant synovitis in comparison to rheumatoid arthritis. Cancer Biother Radiopharm 2005; 20: 349–355.
13. Pommer A. X-ray therapy in veterinary medicine. Adv Vet Sci Comp Med 1958; 4: 97–131.

14. Liebmann A, Hindemith M, Jahns J, et al. Low-dose X-irradiation of adjuvant-induced arthritis in rats. Efficacy of different fractionation schedules. Strahlenther Onkol 2004; 180: 165-172.
15. Hildebrandt G, Radlingmayr A, Rosenthal S, et al. Low-dose radiotherapy (LD-RT) and the modulation of INOS expression in adjuvant-induced arthritis in rats. Int J Radiat Biol 2003; 79: 993–1001.
16. Riggs CM, DeCamp CE, Soutas-Little RW, et al. Effects of subject velocity on force plate measured ground reaction forces in healthy Greyhounds at the trot. Am J Vet Res 1993; 54: 1523-1526.
17. Budsberg SC, Rytz U, Johnston SA. Effects of acceleration on ground reaction forces collected in healthy dogs at a trot. Vet Comp Orthop Traumatol 1999; 12: 15-19.
18. McLaughlin RM, Rousch JK. Effects of subject stance time and velocity on ground reaction forces in clinically normal Greyhounds at the trot. Am J Vet Res 1994; 55: 1666–1671.
19. Nordquist B, Fischer J, Kim SY, et al. Effects of trial repetition, limb side, intraday and inter-week variation on vertical and craniocaudal ground reaction forces in clinically normal Labrador Retrievers. Vet Comp Orthop Traumaol 2011; 24: 435–444.
20. Trott KR, Kamprad F. Radiobiological mechanisms of anti-inflammatory radiotherapy. Radiother Oncol 1999; 51: 197–203.
21. Seegenschmiedt MH, Keilholz L. Epicondylopathia humeri (EPH) and peritendinitis humeroscapularis (PHS): evaluation of radiation therapy long-term results and literature review. Radiother Oncol 1998; 47: 17–28.