

Stereotactic radiosurgery for treatment of osteosarcomas involving the distal portions of the limbs in dogs

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Osteosarcoma is the most common primary bone tumor in dogs.¹ The currently recommended treatment for appendicular osteosarcoma in dogs involves removal of the primary tumor, either through limb amputation or use of various limb-sparing techniques, in combination with adjuvant chemotherapy. However, many dogs are not considered suitable candidates for amputation because of concurrent orthopedic or neurologic conditions, and complications such as implant failure and poor limb function are common when limb-sparing techniques are used to treat tumors involving the humerus, femur, and tibia.^{2,3} Thus, there is growing interest among owners of dogs with appendicular osteosarcoma in alternatives to surgery.

Osteosarcomas were previously thought to be resistant to the effects of radiation therapy. Recent reports,^{4,10} however, indicate that radiation can be an effective method for palliation and some degree of local tumor control, especially when combined with chemotherapy. The reported palliative radiation dose ranges from 3 to 22 Gy, given in multiple fractions. But fractionated radiation therapy requires multiple anesthetic episodes and repeated or prolonged hospitalization, which may make such treatment unfeasible for some owners and dogs.

Through a collaborative effort between the College of Veterinary Medicine's Department of Small Animal Clinical Sciences and the McKnight Brain Institute's Department of Neurosurgery at the University of Florida, the use of **stereotactic radiosurgery (SRS)** for the treatment of various malignant neoplasms in dogs and cats has been studied.¹¹ With SRS, the entire radiation dose is delivered in a single treatment through the use of multiple, noncoplanar beams of radiation that are stereotactically focused on the target.¹² Common indications for SRS in human patients include brain tumors and vascular malformations.¹²

Conventional radiation therapy is performed via a limited number of static fields and relies on the use of fractionation schemes to minimize damage to sur-

rounding healthy tissues.¹³ For example, it is known that a dose of radiation > 4 to 5 Gy given in a single fraction will result in greater damage to late-responding healthy tissues than will the same dose divided into 2 smaller fractions.¹³ In contrast, SRS minimizes damage to healthy surrounding tissues by relying on extreme accuracy of radiation delivery to a tumor and a steep dose gradient between the tumor and surrounding healthy tissues. Advantages of a single large fraction over conventional fractionated therapy include fewer anesthetic episodes and possibly a greater biological effect on tumor tissue, compared with an equivalent total dose delivered in fractions (eg, a single fraction of 30 Gy vs three 10-Gy fractions).¹⁴

To our knowledge, only limited descriptions of the use of SRS for extracranial abnormalities have been published in the human literature, and none of these reports described the use of SRS to treat appendicular abnormalities. As the capacity to correlate the results of various imaging modalities with actual tumor volume has evolved, the ability to target tumor volumes of greater complexity has also developed,¹⁵ meaning that it may now be possible to use SRS to treat appendicular tumors. The purpose of the present report was to describe the use of a frameless, stereotactic radiosurgery system, adapted from a system developed for the treatment of intracranial tumors in human patients,^{12,16,17} for SRS in dogs with appendicular osteosarcomas and report results and complications of the technique in 11 dogs.

Description of the Technique

Dogs were considered candidates for SRS if they had an osteosarcoma involving an appendicular location, the diagnosis of osteosarcoma had been confirmed by means of histologic examination of biopsy specimens, and thoracic radiography did not reveal any evidence of pulmonary metastases. Prior to SRS, a complete diagnostic evaluation was performed, including a CBC, serum biochemistry profile, urinalysis, and limb and thoracic radiography. On the day prior to SRS, the dog was anesthetized and the affected limb was clipped and aseptically prepared for surgery. An array of fiducial markers designed for use as a frameless targeting device^{12,16} was fixed to the affected bone with two 1.6-mm-diameter Kirschner wires placed in a medial-to-lateral direction (**Figure 1**). These Kirschner wires were placed in the mid-diaphyseal portion of the affected bone and cut such that the ends of the wires protruded approximately 2 cm through the skin on either side of the limb. A dental biteplate that could

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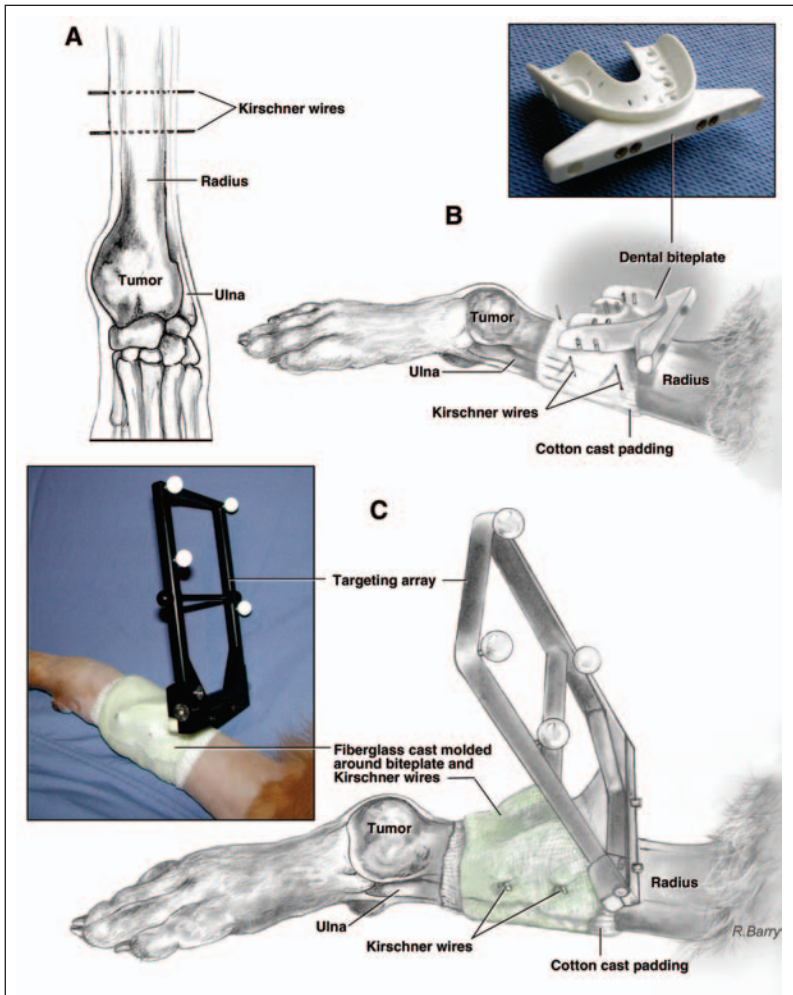


Figure 1—Illustration of a method for using stereotactic radiosurgery to treat an osteosarcoma involving the distal portion of the radius in a dog. A—Two 1.6-mm-diameter Kirschner wires are placed in a medial-to-lateral direction in the mid-diaphyseal portion of the radius and cut such that the ends of the wires protrude approximately 2 cm through the skin on either side of the limb. B—A dental biteplate is secured to the protruding pins with fiberglass casting material; as the casting material hardens, it is molded around the Kirschner wires and dental biteplate to prevent subsequent movement of the biteplate relative to the tumor and affected bone. C—A targeting array is then attached to the biteplate. Fiducial markers on the targeting array allow for stereotactic localization of the array in relation to the tumor during radiation therapy.

easily be attached to and detached from the targeting array was secured to the protruding pins with fiberglass casting material. As the casting material hardened, it was molded around the Kirschner wires and dental biteplate to prevent subsequent movement of the biteplate relative to the tumor and affected bone.

Following attachment of the targeting array to the biteplate, thin-slice (2 mm), contrast-enhanced computed tomographic (CT) images of the entire affected bone, adjacent joints, and array were obtained. The targeting array was then detached from the biteplate, and the affected limb was wrapped with a thick, soft, padded bandage incorporating several layers of roll cotton to protect against possible dislodgment of the biteplate during the time between CT scanning and treatment.

The dog was then allowed to recover from anesthesia and was monitored continuously overnight. Morphine

(0.5 mg/kg [0.23 mg/lb], SC, q 4 to 6 h as needed) was administered for postoperative analgesia. Acepromazine (0.01 mg/kg [0.005 mg/lb], IV, q 4 to 6 h) was administered for sedation if needed.

Computed tomographic images were transferred to the dosimetry planning computer at the McKnight Brain Institute, where a 3-dimensional image of the tumor was created and a treatment plan was generated.^{11,12,17} With SRS, the goal is to deliver a radiation dose in a pattern that conforms to the shape of the target. This is achieved through the use of a linear accelerator to create multiple radiation beams, each with a unique entrance and exit pathway, yet all directed at a single target. The result of the beam overlap, or summation, is a spherical dose volume at the isocenter of the linear accelerator. With irregular target shapes, certain beams are eliminated or changed in shape through the use of collimators so that the radiation dose volume is more elliptical than spherical. The shape of the radiation dose volume can be further modified by repositioning the tumor relative to the isocenter of the linear accelerator.

The treatment plan was generated with a software program developed at the University of Florida.¹⁷ Briefly, fiducial markers in the targeting array were used to calculate the relative position of each pixel on CT images in the X, Y, and Z planes. The target was defined as the contrast-enhanced region on the CT images and a margin of normal-appearing tissue. The margin of normal-appearing tissue varied slightly depending on the size of the mass and its proximity to skin. After the entire target was determined, isocenters of various diameters were designated on the CT images to build a treatment volume that con-

formed to the shape of the tumor (Figure 2). Isodose lines on each CT slice were then evaluated for adequacy of tumor coverage in the sagittal, transverse, and dorsal planes by scrolling through the CT images. Viewing the transverse images from distal to proximal was particularly helpful in making this determination.

Radiation doses that were used were selected on the basis of clinical experience with human patients, doses used in dogs with brain tumors,¹¹ and our preliminary results in dogs with various sarcomas. Treatment plans were initially designed to ensure that the entire contrast-enhanced target (ie, the peripheral border of the tumor and the proximal and distal margins) was included within the 50% isodose shell (ie, minimum dose of 2,000 cGy) and that the central portion of the tumor was included within the 75% isodose shell (ie, 3,000 cGy). In dogs treated later, greater efforts were made to maximize coverage of the tumor

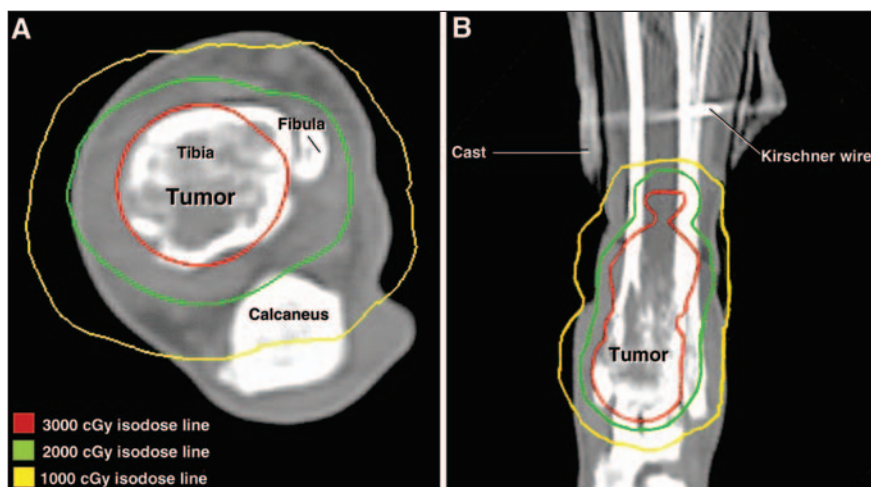


Figure 2—Transverse (A) and dorsal (B) computed tomographic images of the distal portion of the tibia in a dog with appendicular osteosarcoma. The stereotactic radiosurgery treatment plan is superimposed, and the radiation dose distribution is represented by isodose lines. Each image represents only a single slice of the treatment plan.

with the 3,000-cGy isodose shell. In most instances, this involved including margins of bone or joint 2 to 3 cm proximal and distal to the contrast-enhanced region on the CT images. A typical treatment plan required approximately 20 to 30 minutes to create.

The morning following computed tomography, the dog was transported to the McKnight Brain Institute for treatment. Treatment plans were finalized just prior to induction of anesthesia. If desired, carboplatin (300 mg/m², IV) was administered over 20 minutes just prior to initiation of SRS for its potential radiosensitizing effects¹⁸⁻²⁶ and possible effects on micrometastases. The infusion was completed approximately 20 to 30 minutes prior to initiation of SRS.

The targeting array was reattached to the biteplate, and radiation was delivered with a 6-million eV linear accelerator.⁴ The number of treatment arcs ranged from 10 to 26, and the number of isocenters delivered ranged from 3 to 9. Treatment sessions ranged from 40 minutes to 2 hours long. Immediately following treatment, the targeting array, biteplate, and associated pins were removed; the limb was wrapped with a soft-padded bandage; and the dog was allowed to recover from anesthesia. A single dose of morphine (0.5 mg/kg, SC) was given to relieve any pain associated with pin removal.

Each dog was evaluated monthly for the first 3 months after SRS. Minor changes in the skin such as alopecia, whitening of the hair, and moist desquamation were considered adverse effects, whereas problems such as full-thickness skin ulceration and pathologic fractures were considered complications. Limb function was graded as excellent (normal limb function), good (slight lameness only after extensive exercise), fair (slight to moderate lameness but consistent weight-bearing), or poor (non-weight-bearing lameness).²⁷ Follow-up radiographs of the affected limb and thorax (right and left lateral and ventrodorsal projections) were obtained approximately every 3 months. No change in the radiographic appearance of a lesion was considered an indication of stable disease, whereas

measurable tumor enlargement and an increase in bone lysis or production of irregular periosteal new bone, determined subjectively, were considered an indication of tumor progression. If tumor progression was suspected or pulmonary metastases were evident radiographically, additional radiographs were obtained monthly.

Results

Eleven dogs with appendicular osteosarcoma were treated with SRS. This included 3 Golden Retrievers; 2 Labrador Retrievers; 2 mixed-breed dogs; and a Rottweiler, Great Dane, Irish Setter, and Great Pyrenees. Dogs ranged from 7 to 11 years old (median, 9 years) at the time of SRS. The tumor involved the distal portion of the radius in 9

dogs, the distal portion of the ulna in 1, and the distal portion of the tibia in 1. One dog with a tumor involving the distal portion of the radius had a pathologic fracture at the time of initial examination. In this dog, a type II external skeletal fixator was applied and the biteplate was secured to the fixator with 2 short, 3.2-mm-diameter Steinmann pins and 2 double connecting clamps.

Five of the dogs were treated with SRS alone, and 6 were treated with SRS and adjunctive chemotherapy. In all dogs that received chemotherapy, carboplatin was administered just prior to SRS. After SRS, dogs were treated with carboplatin (300 mg/m², IV) every 3 weeks for 4 treatments (2 dogs) or a combination of carboplatin (300 mg/m², IV) and doxorubicin (30 mg/m², IV) alternating every 3 weeks for 4 treatments with each drug (4 dogs).

Physical evaluations were performed monthly for the first 3 months in 10 dogs and every 3 months in 1 dog. In all dogs, tumor-associated swelling and lameness were subjectively improved after SRS, usually within 3 weeks. Radiographic changes seen over time included a moderate reduction in soft tissue swelling in the area and a moderate increase in periosteal new bone formation surrounding the region of osteolysis (Figure 3). Limb function was considered good or excellent in all dogs for the first 3 months after treatment. Although 7 dogs continued to have good limb function after this time, lameness recurred in 4 dogs, all of which were treated with SRS alone, between 3 and 4 months after treatment. The recurrence of the lameness was attributed to a pathologic fracture in 1 dog and progression of the primary tumor in the other 3. Eight (2 treated with SRS alone and all 6 treated with SRS and carboplatin) of the 11 (73%) dogs had stable disease throughout the follow-up period, and 3 (all treated with SRS alone) had evidence of tumor progression (median time to evidence of tumor progression, 105 days).

Overall median survival time, determined by use of the Kaplan-Meier method, was 363 days (range, 145 to 763 days). Six dogs were still alive 90, 142,



Figure 3—Lateral radiographic projections of the distal portion of the radius in a dog with appendicular osteosarcoma. Radiographs were obtained at the time of (A) and 2 years after (B) stereotactic radiosurgery of the tumor. Notice the moderate reduction in soft tissue swelling and moderate increase in periosteal new bone formation surrounding the region of osteolysis. The irregular periosteal response evident at the time of treatment changed to a more regular, smooth appearance over time (arrows).

234, 367, 633, and 763 days after SRS, and limb function was good or excellent in all 6. Five dogs were euthanized (survival time, 145 to 363 days); 1 was euthanized because of progression of the primary tumor, 2 were euthanized because of metastatic disease, and 2 were euthanized because of progression of the primary tumor and metastatic disease.

Adverse effects that were observed include alopecia (7 dogs), desquamation (3), leukotrichia (1), and hyperpigmentation (2). In 1 dog, skin desquamation that was initially observed 4 weeks after SRS progressed to a single small (approx 1 cm in diameter), open skin wound over the craniodistal aspect of the radius approximately 3 months after treatment. Another dog developed a full-thickness skin wound under a splint 1 month after repair of a pathologic fracture that was sustained 4 months after SRS. *Pseudomonas aeruginosa* was recovered from the skin wounds of both dogs. Treatment consisted of wound debridement, surgical closure with a transposition skin flap, and antimicrobial administration.

Four dogs developed a pathologic fracture (mean time to fracture, 5.8 months; range, 3 to 9 months) after undergoing SRS. In 3 of these dogs, the fractures, 2 involving the distal portion of the radius and 1 involving the distal portion of the tibia, were stabilized successfully. Two lag screws were used to stabilize an incomplete articular fracture of the distal portion of the radius, and bone plates were used to stabilize a metaphyseal fracture of the distal portion of the tibia (7 hole, 3.5-mm T-plate) and an articular fracture of the distal portion of the radius (18-hole, 3.5-mm plate spanning the carpal joint). In the 2 dogs in which bone plates were used to stabilize pathologic fractures, limb function was good or excellent and the implants remained in place without complications

during the entire postoperative period. One of these dogs was euthanized because of metastatic disease approximately 6 months after surgery (363 days after undergoing SRS), and the other was alive approximately 1 year after surgery (633 days after undergoing SRS). Histologic examination of a biopsy specimen obtained from one of the radial fractures at the time of stabilization revealed bone necrosis with no evidence of neoplasia. In the fourth dog with a pathologic fracture, the fracture occurred approximately 5.5 months after SRS and was associated with signs of tumor progression. The limb was supported with a splint until the dog was euthanized. The external fixator placed to temporarily stabilize a pathologic fracture of the radius prior to SRS remained in place for 5.5 months. Approximately 6 weeks after the fixator was removed and a splint was placed, definitive fracture stabilization was performed with a hybrid limb-sparing bone plate.^b Definitive stabilization with internal fixation had been delayed because of concerns about potential radiation-induced skin injury.

Discussion

Conventional fractionated radiation therapy has been widely used in the management of appendicular osteosarcoma in dogs.⁴⁻¹⁰ In a previous study,⁸ a fractionated radiation therapy protocol (10 Gy on days 0, 7, and 21) in conjunction with chemotherapy resulted in pain relief in approximately 70% of 95 dogs and a median survival time of 122 days. Mean duration of the pain response was approximately 75 days. A more recent study⁵ found that outcome improved when the number of fractions was increased from 3 to 4. In a separate study,⁶ radiation therapy (24 to 40 Gy) with cobalt 60 in conjunction with intra-arterial administration of cisplatin resulted in a median survival time of approximately 150 days (approx 200 days when dogs with metastases were excluded). In the present report, we describe the treatment of appendicular osteosarcoma with a single large fraction of radiation, with and without chemotherapy, and demonstrate the potential for providing local tumor control.

In the initial 5 dogs described in the present report, the effects of SRS alone were evaluated. In these dogs, the goals during treatment planning were to surround the entire contrast-enhanced region and a margin of normal-appearing tissue with the 2,000-cGy isodose line and to cover a large portion of the tumor with the 3,000-cGy isodose line. Because 3 of these 5 dogs ultimately experienced tumor progression, carboplatin was given approximately 30 minutes prior to SRS in subsequent dogs in an effort to enhance the effects of radiation. Several studies¹⁸⁻²⁶ have indicated that carboplatin has the potential to enhance the effect of radiation on tumors. In addition, we made efforts during treatment

planning to surround as much of the tumor as possible with the 3,000-cGy isodose line. In several dogs, the size, shape, and location of the tumors were such that it was possible to surround the entire lesion with the 3,000-cGy isodose line without exposing the skin to an intolerable radiation dose. Proximity to the skin is the dose-limiting factor for tumors affecting the distal limb bones, as there is little soft tissue between the skin and tumor. Despite the precise nature of SRS, nearby healthy tissues, such as skin, tendons, blood vessels, bone, and nerves, received some radiation, with small portions of the skin receiving up to 2,000 cGy. The skin and connective tissue stroma reportedly can tolerate radiation doses of 1,500 to 2,000 cGy.¹⁵ Although some early radiation injury (erythema and moist desquamation) was observed in the skin of dogs described in the present report, the effects were transient in all but 1 patient. It is possible that this wound could have been prevented from progressing to a full-thickness wound if the owners had been able to prevent self-trauma of the desquamated area by the dog. It is not clear whether a full-thickness wound that developed in a second dog was a result of radiation therapy or a complication of fracture repair and splint management. This wound was first noticed when the bandage holding the splint was being changed and was not preceded by desquamation or other skin changes that would have suggested radiation injury. Both of the full-thickness wounds required surgical treatment for resolution. Because nearby skin proximal and distal to the area of the tumor received little radiation during SRS, local transposition skin flaps were well vascularized and survived following surgical closure of these wounds.

Late effects expected for mature bone exposed to the radiation dose used in dogs described in the present report include osteitis and osteonecrosis.²⁸⁻³⁰ Bone and cartilage reportedly can tolerate doses > 3,000 cGy.^{31,32} Atrophic changes occur in bone as a result of damage to the vessels and cells in the osteoid matrix. This may lead to cell death and, ultimately, to development of an acellular, osseous frame.³³ Radiation therapy has also been shown to make bone more brittle and to reduce energy-absorbing capacity.³⁴ Four dogs in the present report sustained pathologic fractures after undergoing SRS, but pathologic fractures have also been identified in dogs treated with fractionated radiation therapy protocols.^{6,8} One of these dogs had evidence of tumor progression, and it was difficult to determine what role SRS may have played in fracture development. In the remaining 3 dogs, fractures occurred in bones with highly lytic lesions in which there was no radiographic evidence of tumor progression. In these 3 dogs, fractures were stabilized by means of internal fixation. Although a small amount of fracture callous was observed approximately 6 months after fracture stabilization (14 months after SRS) in the dog with a pathologic fracture involving the distal portion of the tibia, radiographic union was still not seen when follow-up radiographs were obtained 11 months after surgery (19 months after SRS). Similarly, there was no evidence of fracture healing 6 months after SRS in the dog with a pathologic radial fracture that was stabilized with an external fixator prior to SRS.

It is possible that in dogs described in the present report in which a complete response was not observed, treatment plans developed solely on the basis of results of computed tomographic imaging may have underestimated the soft tissue component of the tumor peripherally. Ideally, treatment planning for SRS is based on results of computed tomography and magnetic resonance imaging, with images fused on a computer to produce a manipulable 3-dimensional image.¹² Computed tomography provides the most accurate spatial resolution, while magnetic resonance imaging provides greater delineation of anatomic structure, including tumor margins.³⁵ Although computed tomography has been shown to provide an accurate estimation of tumor length in dogs with appendicular osteosarcoma,³⁶ magnetic resonance imaging with contrast is the preferred imaging modality in human patients with osteosarcoma for defining tumor length, the presence of soft tissue involvement, and skip metastases.³⁵ Magnetic resonance imaging was not performed on dogs described in the present report because of limited availability and financial constraints.

We have not yet performed histologic evaluations of SRS-treated lesions because many of the treated dogs described in the present report were still alive. Thus, the assessment of tumor response to SRS is presently based on radiographic and clinical evaluations, and it is not known whether tumors that appeared stable represented partial or complete responses. In dogs that responded favorably, radiographic changes seen over time included a moderate reduction in the tumor-associated soft tissue swelling and a moderate increase in periosteal new bone formation surrounding the region of osteolysis. It was also observed that the periosteal response along the bone cortex changed from an irregular sunburst pattern to a more regular, smooth contour. It is possible that even with complete tumor kill, bone regeneration and remodeling capacity were compromised by radiation therapy, especially in the central area of the lesion where the radiation dose was highest.

Another limitation of the present report is that we were not able to determine the efficacy of SRS alone because chemotherapy was used in dogs treated later in the series. Although the procedure was more successful in these dogs, it is not known whether the improved local tumor control was a result of the addition of chemotherapy or of the experience gained in treatment planning. It is likely that greater local control resulted at least in part from the addition of chemotherapy, as the benefits of chemotherapy with radiation have been reported previously.^{8,10} It would be ideal to more definitively determine the efficacy of SRS alone; however, this may be difficult given the concern for metastatic disease and the need for chemotherapy to control it.

Results in the dogs described in the present report suggest that SRS represents a viable limb-sparing alternative for dogs with appendicular osteosarcoma. Although the findings of the present study are preliminary, complete local control of primary osteosarcoma with a single large fraction appears to be possible. Local tumor control may improve when SRS is combined with chemotherapy; however, it is not known

whether the apparent benefit of adjunctive chemotherapy results from administration of carboplatin prior to SRS, follow-up administration of chemotherapy, or a combination of the two. The degree of local tumor control and median survival time appeared to compare favorably with values reported for other treatment methods.¹⁻³ Application of SRS to tumors of the proximal portions of the limbs and to tumors in axial locations is also feasible with slight modifications of the method used to secure the targeting array to the affected bone. This could potentially offer another treatment alternative for tumors affecting anatomic locations less amenable to limb-sparing surgery (eg, the proximal portion of the humerus). The limiting factors in the use of SRS for appendicular osteosarcomas are the size of the tumor and the condition of the bone at the time of therapy, as adequate coverage of large tumors with the 3,000-cGy isodose line is not always possible and the risk of pathologic fracture remains after treatment. Thus, SRS should ideally be used to treat appendicular osteosarcomas that are relatively small and have caused minimal bone destruction.

^aVarian Medical Systems Inc, Palo Alto, Calif.

^bVeterinary Orthopedic Implants, Buffalo Grove, Ill.

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