Intraoperative Extracorporeal Irradiation for Limb Sparing in 13 Dogs

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Objective—To evaluate extracorporeal intraoperative radiation therapy (IORT) as a treatment method for limb and joint sparing in dogs with appendicular sarcomas in sites other than the distal aspect of the radius.

Study Design—Retrospective study.

Animals—Thirteen client-owned dogs.

Methods—The bone tumor database and medical records (1998–2002) were reviewed for dogs with primary appendicular bone tumors treated with IORT limb-sparing surgery and adjuvant chemotherapy. The segment of bone containing the tumor was isolated from adjacent soft tissue and an osteotomy performed distant to the tumor. The bone segment was exteriorized, irradiated (70 Gy single fraction), and then stabilized with internal fixation. Adjuvant chemotherapy was administered. Lameness was graded and local and distant tumor control was determined. Associations between intra- and postoperative variables with complications and Kaplan–Meier survival analysis for median disease-free interval and survival time were calculated.

Results—Limb function was good or excellent in 10 dogs (77%). Postoperative complications (9 dogs, 69%) included deep infection, fracture of the irradiated bone, and implant failure. Surgical failure was more likely if a single implant was used to stabilize the osteotomized bone and if deep infection developed postoperatively. In 3 dogs, tumors recurred locally within bone in the radiation field. The disease-free and overall success rates of extracorporeal IORT for limb and joint preservation were 46% and 54%, respectively.

Conclusions—Extracorporeal IORT provides a novel alternative to traditional techniques for preservation of joint and limb function in dogs with primary appendicular sarcomas. A minimum of 2 implants and intramedullary bone cement should be used to stabilize the osteotomized bone to minimize postoperative complications. Extracorporeal IORT should be used with caution in dogs with tumors of the distal tibia because of a high complication rate. Dogs with tumors in areas of good soft-tissue coverage, such as the humerus and femur, may be good candidates for limb and joint-sparing surgery using extracorporeal IORT.

Clinical Relevance—Extracorporeal IORT is a surgical technique that can be used for limb and joint salvage in dogs with primary appendicular sarcomas in sites usually not amenable to traditional limb-sparing techniques.

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Key words: extracorporeal intraoperative radiation, limb sparing, appendicular sarcoma, osteosarcoma, dog.
PRIMAR Y APPENDICULAR OSTEOSARCOMA (OSA) is the most common malignancy of bone in dogs. Surgical options for management of the local bone tumor include limb amputation and limb preservation. In dogs, the distal aspect of the radius is the most amenable site for limb-sparing resection and reconstruction because reconstruction of other sites with cortical allografts and concurrent arthrodesis is associated with a high complication rate and poor postoperative limb function. Similar findings have been reported in humans with limb salvage using allograft–arthrodesis. Joint function can be preserved after tumor resection using prostheses, allograft–prosthetic composites, and osteocarticular grafts. However, total joint replacement and joint preservation techniques are not well developed in dogs. Novel alternatives for joint and limb preservation include reimplantation of autografts sterilized by autoclaving, pasteurization, or irradiation.

Intraoperative radiation therapy (IORT) has been investigated in the management of a number of tumors and a modification of this technique, extracorporeal IORT, has been reported in the treatment of primary sarcomas and solitary bone metastasis. Limb sparing with extracorporeal IORT involves wide resection or isolation of the bone tumor, irradiation of the isolated bone segment with a single fraction of 50–300 Gy, removal of extraneous-irradiated soft tissues, and reimplantation and internal fixation of the irradiated bone. There are a number of radiobiologic and clinical advantages in using extracorporeal IORT for limb salvage.

The biologic effect of a single dose of IORT is equivalent to 2–4 times the same dose delivered using fractionated radiation protocols. Furthermore, 50 Gy IORT is tumoricidal to bone tumors and results in complete necrosis of OSA lesions. Experimental studies using single-fraction, high-dose IORT have shown that peripheral nerves, muscle, and skin are particularly sensitive to radiation. In contrast, bone matrix, ligaments, and articular cartilage are relatively resistant to high doses of radiation, which may allow preservation of normal joint and limb function. A principal advantage of extracorporeal IORT is that the radiation field can be focused on the target volume while sparing normal and radiosensitive adjacent soft-tissue structures.

The clinical benefits of limb sparing with extracorporeal IORT include the use of autogenous bone with good anatomic fit, preservation of joint and limb function, and good local tumor control. Our purpose was to retrospectively evaluate surgical technique, local tumor control, and surgical complications using extracorporeal IORT as a novel alternative for limb salvage in dogs with primary appendicular sarcoma.

The bone tumor database and medical records were reviewed for dogs with appendicular sarcomas treated by limb-sparing surgery using extracorporeal IORT between July 1998 and February 2002. Diagnosis of primary bone sarcoma and clinical staging were based on signalment, history, physical examination, hematology and serum biochemistry, regional and 3-view thoracic radiographs, scintigraphy, and histopathologic examination of neoplastic tissue. Clinical staging was based on the Enneking staging system for bone sarcomas where stage I is a histologically low-grade tumor, stage II is a histologically high-grade sarcoma, and stage III sarcomas have evidence of distant metastasis. These stages are then subdivided into A or B, depending on whether the local tumor is intra- or extracompartmental.

Surgical Technique

The surgical approach and techniques were dependent on the anatomic site of the primary bone tumor. Common to all dogs and regardless of the bone involved, the affected site was isolated by dissecting and retracting soft-tissue structures (skin, muscle, nerves, and vessels) away from the tumor while preserving the integrity of the adjacent joint. A needle-core biopsy of the bone lesion was performed for diagnostic purposes before irradiation. The bone was osteotomized a minimum of 2 cm proximal and/or distal to the tumor, as determined primarily by radiographic and scintigraphic imaging, and secondarily by intraoperative examination (Fig 1). At the osteotomy site, bone marrow was collected from the medullary cavity of the bone opposite the tumor segment and submitted for histopathologic evaluation of surgical margins. Extracorporeal IORT was performed either in vivo or ex vivo.

In Vivo Irradiation. A Kirschner wire was inserted perpendicular to the long axis of the bone approximately 1 cm from the osteotomy site on the tumor side of the bone (Fig 2). The surgical site was protected with moistened laparotomy sponges and sterile drapes, and the anesthetized dog was transported to the radiation suite. The segment of bone containing the tumor was exteriorized by suspending the bone within the beam of a 6 MV linear accelerator (Mevatron 6740, Siemens, Concord, CA) using sterile umbilical tape from the Kirschner wire to a ceiling hook. The isolated soft-tissue structures were retracted from the planned radiation site with towel clamps and sutures. A 1.5–2.0 cm sterile tissue-equivalent bolus was wrapped around the exposed bone and also secured with towel clamps. The beam was collimated on the exteriorized bone tumor with the radiation field extending from immediately below the Kirschner wire to the adjacent joint, including articular cartilage. 70 Gy of 6 MV photons was delivered to the bone segment with a single beam using source-to-skin distance geometry. After completion of radiation therapy, the exteriorized bone was replaced and protected with moistened laparotomy sponges and sterile drapes, and the dog was returned to the surgery theater for stabilization of the osteotomy site.
Ex Vivo Irradiation. The resected bone segment was placed in a sterilized zip lock bag filled with sterile saline (0.9% NaCl) solution and transported to the radiation suite. The bone segment and zip lock bag were placed in a plastic container and covered with a 1.0–1.5 cm tissue-equivalent bolus. The entire bone segment was irradiated with a single beam, using source-to-skin distance geometry, with a single 70 Gy fraction of 6 MV photons. The bone segment was returned to surgery where it was aseptically removed from the zip lock bag and placed into the surgical site.

In surgery, irradiated extraperiosteal tumor and soft tissue were removed and, in some dogs, the medullary cavity of the autograft was filled with tobramycin- and vancomycin-impregnated polymethylmethacrylate (PMMA). The osteotomized bone was then stabilized using one, or a combination of, dynamic compression plate (DCP), interlocking nail (ILN), and intramedullary pin. In some dogs, a biodegradable implant containing 8% cisplatin (open-cell polyactic acid [OPLA-Pt], Kensey Nash Corporation, Exton, PA) was implanted into the surgical wound adjacent the irradiated tumor. A closed continuous suction drain was maintained at the surgery site for 12–48 hours in all dogs and operated limbs were protected with soft-padded bandages for up to 5 days. Postoperative activity was restricted to leashed exercise for 4 weeks and then followed by unlimited exercise. Exercise was not prohibited as controlled activity improves peripheral circulation and minimizes the risk of developing edema of the foot and contracture of the digit flexor tendons.

Adjuvant Chemotherapy

Chemotherapy was administered to all dogs starting 10–21 days after limb-sparing surgery. Chemotherapy protocols involved single- or dual-agent therapy with intravenous [IV] cisplatin, doxorubicin, or carboplatin, or an investigational slow-release formulation of subcutaneous cisplatin. Evaluation of limb function and regional and thoracic radiographs were recommended monthly for the first 3 months, then every 3 months for 12 months, and every 6 months thereafter.

Limb Use

Lameness was subjectively graded as absent, mild, moderate, or severe, depending on the degree and duration of weight-bearing on the operated limb. Lameness was graded as mild if weight bearing and present when running but not at either the walk or trot, moderate if the lameness was weight-bearing and present during all levels of activity, and severe with a non-weight-bearing lameness. Limb function was considered excellent if lameness was absent, good with mild lameness, and poor if lameness was either moderate or severe.

Data Analysis

Limb use, surgical complications, radiation-induced effects, local tumor recurrence, metastasis, disease-free interval, and survival time were recorded. The percentage of dogs with an intact limb-spare at the time of death or termination of the study, with and without regard to local tumor recurrence, was calculated and defined as the disease-free and overall limb-salvage rate, respectively. Disease-free interval and metastasis-free interval were defined as the time from limb-sparing surgery to the detection of local tumor recurrence or distant metastasis, respectively. Survival time was defined as the time from surgery to either death or euthanasia. Median disease- and metastasis-free intervals and survival time were calculated using Kaplan–Meier survival analysis with log rank. χ² test was used to assess the relationship of local tumor recurrence,
failure of irradiated bone, and failure of surgical implants with bone tumor location, type and number of surgical implants, use of PMMA and OPLA-Pt, and postoperative infection. For all comparisons, a \( P \)-value <.05 was considered significant.

**RESULTS**

Thirteen dogs had limb-sparing surgery performed using a combination of extracorporeal IORT and surgical stabilization. The signalment was typical for dogs with appendicular OSA: large breed and middle to older aged. A number of breeds were represented, including 3 each of Labrador Retriever and Rottweiler, with a median body weight of 45 kg (range, 28–91 kg). The median age at admission was 9 years (range, 3–10 years). Two dogs were female and 11 were male. Varying degrees of lameness, ranging from mild to non-weight-bearing, were evident in all dogs for a median of 6 weeks (range, 0.3–33 weeks) before admission.

All dogs were staged by hematology, serum biochemistry, regional and 3-view thoracic radiographs, and scintigraphy. Hematologic abnormalities were non-specific and included mild thrombocytopenia in 2 dogs. One dog had elevated concentrations of all liver enzymes whereas 2 dogs had elevated serum concentrations of alkaline phosphatase.

**Diagnostic Imaging**

Radiographic changes typical of a primary bone tumor were seen in all affected limbs. Bones and sites involved were: radius (n = 1, mid-diaphyseal), humerus (5; 1 mid-diaphyseal, 4 proximal metaphyseal), tibia (6; 1 mid-diaphyseal, 5 distal metaphyseal), and femur (1, distal metaphyseal). Five tumors were left sided and 8 were right sided. Whole-body scintigraphy showed disease confined to the affected limb in all but 1 dog where skeletal lesions were detected in both the mid-diaphysis of the tibia and distal metaphysis of the contralateral radius.

**Surgical Technique**

The surgical approach was standard for each location with a dorsal approach to the radius, medial approach to the tibia, and lateral approaches to both the humerus and femur. Soft-tissue structures were marginally dissected away from the bone before osteotomy. In particular, regional peripheral nerves were identified, isolated, and gently retracted with sterile umbilical tape. Osteotomies were performed either distal (n = 4) or proximal (7) to the lesion for in vivo irradiation, depending on tumor location, or both distal and proximal to the tumor for intercalary resection and ex vivo irradiation (2).

After IORT, osteotomies were stabilized with internal fixation. The medullary cavity of the irradiated bone was filled with antibiotic-impregnated PMMA in 7 dogs. OPLA-Pt was implanted adjacent to irradiated bone in 4 dogs.

**In Vivo IORT.** Eleven dogs had osteotomies performed either proximal or distal to metaphyseal sarcomas for in vivo extracorporeal IORT.

- **Humeral osteotomy:** Humeral osteotomies were stabilized with a narrow (n = 3) or broad (2) 3.5 mm DCP. In 4 dogs, the bone plate was combined with an intramedullary pin (3) or ILN (1).
- **Tibial osteotomy:** Tibial osteotomies were stabilized with a 6 or 8 mm ILN (2), broad 3.5 mm DCP (1), or a combination of an 8 mm ILN and narrow 3.5 mm DCP (2).
- **Femoral osteotomy:** The femoral osteotomy was stabilized with an 8 mm ILN and narrow 4.5 mm DCP.

**Ex Vivo IORT.** Two dogs had osteotomies performed proximal and distal to mid-diaphyseal sarcomas for intercalary resection and ex vivo extracorporeal IORT.

- **Radial osteotomies:** The radial osteotomies were stabilized with 2 stacked 2.0/2.7 mm veterinary cuttable plates at 90° to each other and spanning both osteotomies.
- **Tibial osteotomies:** A single broad 3.5 mm DCP was used to stabilize both tibial osteotomies. In this dog, a synchronous second lesion in the distal radius was resected and limb-sparing performed with a cortical allograft and pancarpal arthrodesis.

**Operative Time**

The median operative time was 365 minutes (range, 187–635 minutes) and median duration of post-surgical hospitalization was 2 days (range, 1–4 days).

**Histopathology**

Diagnoses were undifferentiated sarcoma in 1 dog and high-grade OSA in 12 dogs. Osteotomy was performed through normal bone in all cases with no evidence of tumor in bone marrow samples. According to the Enneking system for the staging of soft-tissue and bone sarcomas, these dogs were systemically staged with IIA (n = 3), IIB (9), and stage III (1) disease.

**Postoperative Care**

All dogs were administered analgesics and antibiotics. Analgesics included oral morphine (0.5–1.0 mg/kg every 8–12 hours) or transdermal fentanyl for 3–5 days and
non-steroidal anti-inflammatory drugs, such as piroxicam (0.3 mg/kg once daily) or carprofen (2.2 mg/kg every 12–24 hours), for 10–21 days. First-generation cephalosporins were administered throughout chemotherapy and continued for a further 4 weeks after completion of chemotherapy, unless a surgical infection was present and culture results necessitated a change in antibiotics (n = 3).

Limb Use

Limb function was subjectively assessed at various time intervals postoperatively (13–1775 days). Lameness was assessed before onset of complications in dogs where limb amputation was performed for treatment of the complication (n = 4). Lameness was absent in 4 dogs, mild and intermittent in 6 dogs, moderate in 2 dogs, and non-weight-bearing in 1 dog. Thus, limb function was excellent in 4 dogs, good in 6 dogs, and poor in 3 dogs.

Chemotherapy

Dogs were targeted to receive 4 doses of carboplatin (4 dogs), 5 doses of cisplatin (1), 5 doses of doxorubicin (2), 3 doses each of carboplatin and doxorubicin in an alternating drug protocol (4), or 1–2 doses of an experimental subcutaneous, slow-release formulation of cisplatin (2). Chemotherapy IV was planned to start at 10–14 days and administered every 3 weeks until completion of the targeted course. Five dogs did not complete their targeted chemotherapy course because of either local failure (1) or metastatic disease (4). One dog was administered 1 dose each of carboplatin and doxorubicin before detection of metastasis to the regional lymph node and lungs, and was changed to subcutaneous cisplatin without beneficial effect.

Surgical Complications (9 dogs, Table 1)

Fracture of the irradiated bone was diagnosed in 7 dogs, implant failure in 5 dogs, infection in 3 dogs, and transient partial radial nerve paralysis in 1 dog (Table 1) for an overall complication rate of 69%. Five dogs had more than 1 complication. Infection was diagnosed in 3 dogs 28, 35, and 139 days postoperatively. *Pseudomonas aeruginosa* and *Bacteroides uniformis* were cultured from the first dog, *Enterococcus faecalis* from the second dog, and a variety of aerobic and anaerobic organisms, such as *Staphylococcus*, *Prevotella*, *Porphyromonas*, and *Pectostreptococcus* spp. in the third dog.

In the first dog, infection was unresponsive to treatment with oral enrofloxacin and ampicillin, and implantation of PMMA beads impregnated with tobramycin and vancomycin into the infection site. Infection persisted for a further 42 days until limb amputation was performed as a result of implant failure. Infection resolved in the second dog after removal of 3 broken screws. In the third dog, the infection eventually resolved after 21 weeks of treatment with various antimicrobial agents, including cephalixin, metronidazole, and antibiotic-impregnated PMMA beads. Failure of limb salvage with subsequent amputation was significantly more likely with the development of a deep infection in the postoperative period.

Table 1. Tumor Location, Surgical Complications, and Radiation-Induced Effects in 13 Dogs Treated with Extracorporeal Intraoperative Radiation Therapy and Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Dog</th>
<th>Bone</th>
<th>Site</th>
<th>Complications</th>
<th>Treatment</th>
<th>Radiation Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Humerus</td>
<td>Proximal</td>
<td>Fracture, diaphyseal</td>
<td>Revision</td>
<td>Bone resorption</td>
</tr>
<tr>
<td>2</td>
<td>Humerus</td>
<td>Proximal</td>
<td>Fracture, metaphyseal</td>
<td>Revision</td>
<td>Bone necrosis</td>
</tr>
<tr>
<td>3</td>
<td>Humerus</td>
<td>Proximal</td>
<td>Fracture, diaphyseal</td>
<td>Revision</td>
<td>Bone necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Tibia</td>
<td>Distal</td>
<td>Infection</td>
<td>Antibiotics</td>
<td>Muscle fibrosis</td>
</tr>
<tr>
<td>5</td>
<td>Femur</td>
<td>Distal</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Tibia</td>
<td>Distal</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Humerus</td>
<td>Diaphyseal</td>
<td>Implant failure</td>
<td>Amputation</td>
<td>Bone necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infection</td>
<td>Antibiotics</td>
<td>Muscle fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radial nerve paralysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Humerus</td>
<td>Proximal</td>
<td>Fracture, osteotomy</td>
<td>Revision then amputation</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fracture, osteotomy</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infection</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Tibia</td>
<td>Diaphyseal</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Tibia</td>
<td>Distal</td>
<td>Fracture, osteotomy</td>
<td>Amputation</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>Radius</td>
<td>Diaphyseal</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Tibia</td>
<td>Distal</td>
<td>Fracture, metaphyseal</td>
<td>Revision</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>Tibia</td>
<td>Distal</td>
<td>Fracture, metaphyseal</td>
<td>Revision then amputation</td>
<td>Bone resorption</td>
</tr>
</tbody>
</table>
\(P = .033\), although there were no significant associations between infection and the intraoperative use of PMMA \(P = .416\) or OPLA-Pt \(P = .913\).

Surgical failure, defined as either fracture or implant failure, was treated with either revision or limb amputation. The median time to surgical failure was 72.5 days (range, 13–172 days). All dogs with pathologic fracture of the irradiated bone had revision surgery. In 3 dogs with fracture of the metaphyseal bone of the humerus, the intramedullary pin was removed and replaced with an ILN. DCPs were preserved in all cases because the bone fractured either proximal or distal to the plate and did not affect the structural integrity of the DCP. Revision was successful in all dogs with humeral fractures. Three dogs were diagnosed with combined fracture of the distal tibial metaphysis and implant failure (Fig 3). In 2 of these dogs, surgical revision was performed with the addition of a narrow or broad 3.5 mm DCP to the original 8 mm ILN. Revision failed in both dogs because of progressive fracture and collapse of the irradiated metaphyseal bone resulting in limb amputation and euthanasia in 1 dog each. Amputation was performed as primary management for the third dog with failure of distal tibial limb-sparing surgery.

Local implantation of OPLA-Pt adjacent the tumor site had a significant association with all bone failures \(P = .009\), regardless of whether diaphyseal or metaphyseal, but not when diaphyseal \(P = .109\) or metaphyseal \(P = .188\) fractures were evaluated separately. A significant association was identified between metaphyseal failure and the use of a single ILN for post-IORT stabilization of the osteotomized bone \(P = .017\). No other significant relationships were identified between the examined variables and metaphyseal, diaphyseal, and all bone fractures.

Implant failure occurred in 5 dogs. Failure occurred as a result of screw, plate, and ILN breakage in 2 dogs with humeral OSA. In 3 dogs with distal tibial metaphyseal OSA, bending of the distal ILN screw (1) and screw pullout (2) most likely occurred secondary to pathologic fracture and collapse of irradiated metaphyseal bone. Amputation was performed in 2 dogs and revision was attempted in 3 dogs with the application of an additional DCP. In 1 dog with a proximal humeral OSA, the surgical implants failed on 2 further occasions and amputation was performed after the third implant failure. Limb amputation and euthanasia were performed in the remaining 2 dogs with distal tibial OSA as a result of further fracture and collapse of the irradiated bone.

An association between implant failure and use of a single implant \(P = .053\), particularly a single ILN \(P = .076\), to stabilize the osteotomy after IORT and local implantation of OPLA-Pt adjacent to the surgery site \(P = .057\) approached significance. Overall, limb and joint function were preserved in 7 dogs (53.8%; humerus, 3; tibia, 3; radius, 1) with 4 of these dogs not requiring revision surgeries, including both dogs with intercalary resections. The association between intercalary resection and a successful, revision-free limb-salvage approached significance \(P = .052\).

**Radiation-Induced Effects (8 Dogs, Table 1)**

Bone biopsy was performed in all dogs with surgical failure and histopathologic changes noted were resorption (n = 4), necrosis (3), and fibrosis (1) of the irradiated bone. Other radiation effects included acute skin necrosis (1) and late muscle fibrosis (2).

**Disease-Related Adverse Effects (7 Dogs, Table 2)**

Local tumor recurrence was detected in bone within the radiation field in 3 dogs treated with in vivo IORT.
with a median time to local recurrence of 274 days (range, 145–310 days), 1 incidentally at postmortem and 2 antemortem. Local recurrence was treated with limb amputation in 2 dogs alive at the time of diagnosis. Both dogs were euthanatized, 23 and 59 days after limb amputation, because of skeletal metastases.

Metastatic disease was diagnosed in 7 dogs, including all 3 dogs with presumed local tumor recurrence, with a median time to metastasis of 116 days (range, 99–369 days). Pulmonary metastases were detected 99 days after double limb-sparing surgery in 1 dog with synchronous disease at the time of diagnosis. Metastatic sites included lungs (n = 5), skeleton (2, humerus and vertebra), lymph node (1), and skin (1). Three dogs were alive and disease-free 556–1775 days postoperatively. Of these dogs, 2 were alive with preservation of limb and joint function and 1 was alive but with an amputated limb as a result of surgical complications. Seven dogs died or were euthanatized as a result of tumor-related causes (metastasis), 1 dog because of surgical complications (local implant failure and pathologic fracture), and 2 dogs from unrelated causes (metastatic leiomyosarcoma, 1; unspecified pain, 1). The disease-free and overall limb- and joint-salvage rates for extracorporeal IORT were 46% and 54%, respectively. The median survival time for dogs with appendicular sarcoma treated with limb- and joint-sparing extracorporeal IORT was 298 days (range, 116–1775 days).

**DISCUSSION**

Thirteen dogs were diagnosed with a primary bone sarcoma and treated with extracorporeal IORT and adjuvant chemotherapy. Their presentation was typical of dogs with appendicular OSA as most were large breed and middle-aged, with tumors in a metaphyseal location and no evidence of metastatic disease. One dog had stage III disease with synchronous or metastatic OSA of the mid-tibia and contralateral distal radius.

Extracorporeal IORT was used to treat the local bone tumor as alternative limb-sparing techniques are often associated with unsatisfactory results because of implant failure or poor limb function. Limb function was subjectively assessed up to 1775 days postoperatively with 10 dogs having good to excellent limb use, whereas 3 dogs had poor limb function with either marked weight-bearing or non-weight-bearing lameness. This evaluation was limited by the subjective criteria used for assessing the degree and duration of lameness, assessment of lameness before onset of surgical complications, and the retrospective design of our study. However, the 77% rate of good limb function was similar to the 69–90% reported in dogs with allograft-arthrodesis of distal antebrachial tumors. Human studies also report good to excellent limb function after limb-sparing with extracorporeal IORT.

Complications occurred in 9 dogs (69%) as a result of surgery or IORT. Pathologic fracture of the irradiated bone was diagnosed in 7 dogs and is a common complication with the use of irradiated bone autografts and allografts in human oncologic surgery.

Radiation-induced changes in the cellular and vascular elements of bone result in osteopenia, decreased mechanical strength, and an increased risk of pathologic fracture and implant failure. Cellular changes include loss of osteoprogenitor cells, osteoblasts, osteoclasts, and osteocytes. These changes may be caused by either a direct cytotoxic effect or secondary to obstruction of blood vessels. Vascular changes are progressive with histologic abnormalities such as obliterator endarteritis and periarteritis, endothelial cell swelling.

### Table 2. Local Recurrence, Metastasis, and Survival Time in 13 Dogs with Primary Bone Sarcomas Treated with Extracorporeal Intraoperative Radiation Therapy and Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Dog</th>
<th>Diagnosis</th>
<th>Stage</th>
<th>Recurrence</th>
<th>DFI (days)</th>
<th>Metastasis</th>
<th>MFI (days)</th>
<th>Survival (days)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sarcoma</td>
<td>IIA</td>
<td>No</td>
<td>—</td>
<td>No</td>
<td>—</td>
<td>&gt;1775</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>OSA</td>
<td>IIB</td>
<td>No</td>
<td>—</td>
<td>Lung</td>
<td>116</td>
<td>116</td>
<td>Metastasis</td>
</tr>
<tr>
<td>3</td>
<td>OSA</td>
<td>IIB</td>
<td>Yes</td>
<td>274</td>
<td>Lung and node</td>
<td>75</td>
<td>274</td>
<td>Metastasis</td>
</tr>
<tr>
<td>4</td>
<td>OSA</td>
<td>IIB</td>
<td>Yes</td>
<td>310</td>
<td>Bone</td>
<td>369</td>
<td>373</td>
<td>Metastasis</td>
</tr>
<tr>
<td>5</td>
<td>OSA</td>
<td>IIB</td>
<td>Yes</td>
<td>145</td>
<td>Bone</td>
<td>168</td>
<td>189</td>
<td>Metastasis</td>
</tr>
<tr>
<td>6</td>
<td>OSA</td>
<td>IIB</td>
<td>No</td>
<td>—</td>
<td>No</td>
<td>—</td>
<td>294</td>
<td>Unrelated metastatic leiomyosarcoma</td>
</tr>
<tr>
<td>7</td>
<td>OSA</td>
<td>IIA</td>
<td>No</td>
<td>—</td>
<td>Lung and skin</td>
<td>280</td>
<td>298</td>
<td>Metastasis</td>
</tr>
<tr>
<td>8</td>
<td>OSA</td>
<td>IIB</td>
<td>No</td>
<td>—</td>
<td>No</td>
<td>—</td>
<td>&gt;1344</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>OSA</td>
<td>III</td>
<td>No</td>
<td>—</td>
<td>Lung</td>
<td>99</td>
<td>198</td>
<td>Metastasis</td>
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<tr>
<td>10</td>
<td>OSA</td>
<td>IIB</td>
<td>No</td>
<td>—</td>
<td>Lung</td>
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<tr>
<td>11</td>
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<td>—</td>
<td>No</td>
<td>—</td>
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<td>12</td>
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<td>—</td>
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<td>—</td>
<td>232</td>
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<td>IIB</td>
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<td>—</td>
<td>No</td>
<td>—</td>
<td>332</td>
<td>Unspecified pain</td>
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OSA, osteosarcoma.
and vacuolization, collagenous hyalinization, and thickening of the tunica media. These changes result in progressive narrowing of blood vessel lumens and decreased vascular volume, blood flow, and oxygen tissue tension. Radiation-induced vascular changes are more marked after administration of a single large dose of radiation compared with equivalent doses using fractionated protocols. Ischemia and loss of cellular elements results in increased bone porosity, reduced new bone formation and remodeling, and decreased mechanical strength. Furthermore, repair of radiation induced bone damage is delayed by high-dose radiation. The combination of reduced resistance to biomechanical forces and delayed repair of radiation damage results in a disproportionate load distribution through the orthopedic implants used to stabilize osteotomized and irradiated bone and an increased risk of fracture and implant failure.

Pathologic fracture occurred in 7 dogs treated with in vivo extracorporeal IORT but in none of the dogs with ex vivo extracorporeal IORT. Similarly, intercalary limb sparing using cortical allografts is often associated with fewer postoperative complications and better limb function than limb salvage using allograft–arthrodesis, allograft–prosthesis, or ostearticular techniques. Potential causes for pathologic fracture include radiation-induced osteoporosis, pre-existing tumor-induced osteolysis, and local tumor progression. However, progression or recurrence of the local tumor was unlikely in our dogs, as concurrent local failure and pathologic fracture were not diagnosed. Fracture of primary humeral sarcomas was successfully revised in all 3 dogs by supplementing the original DCP with an ILN.

Pathologic fracture and metaphyseal collapse were associated with implant failure in a further 3 dogs with distal tibial OSA. In contrast to pathologic fractures of irradiated humeri, attempted revision of tibial fractures failed because of progressive metaphyseal collapse and were eventually salvaged with limb amputation. A significant association was identified between metaphyseal failure and the use of a single ILN. Furthermore, implant failure was more likely with the use of a single implant, particularly an ILN, to stabilize the osteotomy site. On the basis of these results, a minimum of 2 implants, whether a combination of an ILN and DCP, or 2 DCP perpendicular to each other, are recommended for the stabilization of osteotomies after IORT, particularly if the irradiated tumor is located in the metaphyseal region of the distal tibia.

Orthopedic plates and ILN are appropriate devices for fixation of osteotomies as both result in similar rates and types of healing in animal models using an intercalary allograft. In humans, the risk of pathologic fracture is significantly reduced by combining IORT with prosthetic joint replacement as the combination of intramedullary fixation with a stem and PMMA protects the irradiated bone from repeated stresses and fatigue fracture. Intramedullary PMMA significantly decreases the incidence of allograft fracture and screw pullout in dogs with allograft–arthrodesis of distal antebrachial tumors. In contrast, the use of PMMA did not reduce the incidence of fracture in irradiated bone in our dogs. Fracture occurred through metaphyseal bone in 2 dogs and this region lacks a medullary canal and is therefore not protected by the PMMA column. Intramedullary PMMA does not adversely affect the healing of intercalary allografts and was not associated with surgical failures in the present series.

By contrast, there was a significant association between the local implantation of OPLA-Pt adjacent to the irradiated tumor and subsequent bone fracture and implant failure. Cisplatin released from OPLA is cytotoxic and, despite reducing the rate of local recurrence after tumor resection, does increase the risk of allograft-host bone non-union after intercalary resection (J.M. Liptak, unpublished data). However, OPLA-Pt has not previously been associated with catastrophic failure in dogs treated with allograft–arthrodesis limb salvage. The combination of radiation and local chemotherapy may be sufficiently cytotoxic to suppress normal bone healing. As a result, irradiated bone is more susceptible to fracture and implant failure may be more likely as the internal fixation devices are required to support a disproportionate amount of the weight-bearing load.

Revascularization of bone is important in the repair of radiation-induced bone porosity and reducing the risk of pathologic fracture. We found that dogs with tumors in the diaphysis and upper extremity had a better postoperative outcome and rate of limb salvage than dogs with tumors of the distal extremity, particularly the distal tibia. Soft-tissue coverage of the diaphysis and upper extremity is superior to the distal extremities and may provide a better source of extraosseous and periosteal vessels required for revascularization of bone. The use of muscle flaps should be considered after extracorporeal IORT of distal extremity lesions to enhance revascularization of irradiated bone and potentially decrease the risk of pathologic fracture.

Surgical infections were diagnosed in 3 dogs during the chemotherapy course while being treated with prophylactic antibiotics. Antibiotic elution from PMMA did not protect against postoperative infection and the local release of cisplatin from OPLA-Pt was not significantly associated with deep infection. Infection is a common complication in dogs with allograft–arthrodesis of the glenohumeral and antebrachiocarpal joints, and is often refractory to management with systemic antibiot-
A similar incidence of deep infection has also been reported after extracorporeal IORT in humans.\textsuperscript{10,17,19} Furthermore, radiation decreases the resistance of bone to infection and may increase the risk of osteorADIO-
necrosis.\textsuperscript{30} The pathophysiologic mechanisms involved in deep infection after massive allografting in dogs and hu-
mans is poorly understood and prevention with intrao-
operative, local, and prolonged postoperative antimicrobial
therapy is often unrewarding.\textsuperscript{1} However, the importance
of preventing deep postoperative infection is highlighted
by the significant association between infection and fail-
ure of limb-salvage in our dogs.

Acute and late radiation effects were suspected in 8
dogs (62%). Inadvertent inclusion of a section of skin in
the radiation field during IORT was suspected in 1 dog
because of the appearance of full-thickness skin ulcer-
atión and necrosis 21 days postoperatively. One dog was
diagnosed with partial radial nerve paralysis although
retraction of the radial nerve was the most likely cause
of this palsy as neurologic deficits were noted immediately
postoperatively and resolved within 16 days. In contrast,
radiation-induced peripheral neuropathy is a late effect
resulting in complete loss and poor recovery of neuro-
logic function.\textsuperscript{13,21} Severe peripheral neuropathy is a
common problem after in situ IORT of bone sarcomas,
including all soft-tissue structures within the surgical bed,
and emphasizes the need to dissect and retract uninvolved
soft tissue away from the radiation field.\textsuperscript{13}

Muscle fibrosis was detected within the radiation field
in 2 dogs and is a common complication after extra-
corporeal IORT in humans.\textsuperscript{13} Increased bone porosity,
because of either resorption or necrosis, is a well-
recognized late effect of IORT and was diagnosed in 6
dogs.\textsuperscript{10,17,22,23,25,29,30} Bone resorption and necrosis were
only diagnosed in dogs undergoing revision for implant
failure or pathologic fracture and is probably more prev-
alent than suggested by these findings.

Local tumor recurrence was suspected in 3 dogs (23%)
after in vivo IORT. In animal and human studies, a single
fraction \( \geq 50 \text{ Gy} \) is considered tumoricidal.\textsuperscript{15} The rate of
local recurrence in human bone tumors treated with ex-
tracorporeal IORT is very low with the majority occur-
rning outside the radiation field in either adjacent soft
tissues or non-irradiated bone.\textsuperscript{9–19} In our dogs, however,
local recurrence occurred in bone within the radiation
field. Two dogs were diagnosed antemortem with local
tumor recurrence although metastatic disease to the irra-
diated site cannot be excluded as distant skeletal met-
astases were diagnosed in both dogs within 60 days of
local recurrence. Furthermore, OPLA-Pt was implanted at
the surgical site in both of these dogs and OPLA-Pt sig-
nificantly reduces the risk of local tumor recurrence in
dogs with allograft-arthrodesis of the antebrachiocarpal
joint.\textsuperscript{30}

The position of the osteotomy in relation to the bone
tumor was primarily determined by radiography and nu-
clear scintigraphy. These imaging modalities overestimate
the degree of bone involvement in dogs with appendicular
OSA and increase the likelihood of complete surgical re-
section when the osteotomy is planned on these findings,
as was achieved in all dogs based on histopathologic in-
terpretation of bone marrow samples.\textsuperscript{42,43} The cause of
local recurrence in dogs is unknown, as tumoricidal doses
were administered to completely resected bone. Possibil-
ities include failure to completely include the bone tumor
in the radiation field, radiation dose of 70 Gy may not be
tumoricidal in dogs, the tumoricidal effects of radiation
may be reduced by tumor volume, and that metastatic
disease was misdiagnosed as local recurrence.

Chemotherapy was administered to all dogs, although
5 dogs failed to complete their targeted course because of
disease-related adverse events. Distant metastasis to either
the lungs or skeleton was diagnosed in 7 dogs with a me-
dian metastasis-free interval of 116 days. Three dogs were
alive and disease-free 556–1775 days postoperatively, in-
cluding 1 dog with an undifferentiated sarcoma, and 7
dogs were dead or euthanatized as a result of tumor-re-
lated causes. The median survival time for dogs treated
with extracorporeal IORT and adjuvant chemotherapy
was 298 days, which is within the range of survival times
reported for dogs with appendicular OSA treated with
either limb amputation or sparing and chemotherapy.\textsuperscript{1–3,40}

Extracorporeal IORT was performed in 13 dogs with
primary bone sarcomas as a novel method to preserve
joint and limb function. Limb function was good to ex-
cellent in most dogs. Surgical complications, such as
pathologic fracture and implant failure, were common
and, except for fracture of the irradiated humerus, limb
amputation was frequently required for salvage of these
adverse events. Radiation decreases the mechanical
strength of bone through resorption and necrosis, and
predisposes to pathologic fracture.\textsuperscript{22,30,31} The use of
PMMA to support the structural integrity of bone, par-

cularly during repair phase of radiation damage, may
reduce the rate of implant failure in diaphyseal regions\textsuperscript{38}
although the efficacy in metaphyseal bone is unknown.
Local tumor control, metastatic rate, and overall survival
were similar to other reports of dogs with appendicular
OSA treated with limb-sparing surgery and adjuvant
chemotherapy.\textsuperscript{1–3} The tumor-free and overall success
rates of extracorporeal IORT for limb and joint preser-
vation in dogs were 46% and 54%, respectively. Extracorporeal IORT is a novel technique for joint
and limb salvage and may be indicated for diaphyseal
tumors and metaphyseal sarcomas with good soft-tissue
coverage.
REFERENCES


