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Intercalary Bone Grafts for Joint and Limb Preservation in 17 Dogs with High-Grade Malignant Tumors of the Diaphysis

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Objective—To evaluate postoperative complications, limb function, and tumor control after intercalary resection and reconstruction for preservation of limb and joint function in dogs with high-grade malignant tumors of diaphyseal bone.

Study Design—Retrospective study.

Animals—Seventeen client-owned dogs.

Methods—The bone tumor database and medical records were reviewed (1986–2002) for dogs with diaphyseal tumors treated with intercalary resection and reconstruction with either an allograft or irradiated autograft. Clinical presentation, diagnostic findings, surgical management, and outcome were determined from medical records and telephone interviews with veterinarians and owners. Statistical analyses included χ^2 to test associations between intra- and postoperative variables with complications, and Kaplan–Meier survival analysis for disease-free interval, metastasis-free interval (MFI), and median survival time.

Results—Intercalary limb-sparing surgery was performed in 17 dogs with diaphyseal tumors: osteosarcoma (OSA) (15), histiocytic sarcoma (1), and solitary metastasis from a pulmonary adenocarcinoma (1). One dog was excluded from further analysis when the spared limb was amputated 4 days postoperatively because of incomplete tumor resection. In 16 dogs, limb function was good to excellent. Complications occurred in 5 dogs (31.3%) and included superficial infection in 2 dogs (12.5%) and implant failure in 4 dogs (25%). All implant failures occurred in the ulna and there was a significant association between implant failure and non-cemented allografts ($P = .042$). Non-union of 1 or both osteotomies was diagnosed in 10 dogs (83.3%) and, despite lack of clinical signs in all cases, was significantly associated with the use of intracavitary locally released cisplatin ($P = .046$) and cemented intercalary grafts ($P = .046$). Local tumor recurrence was diagnosed in 1 dog (6.3%) and metastatic disease in 12 dogs (75.0%), including 10 dogs with OSA. The median MFI was 137 days. The local disease-free and overall limb-salvage rate was 94% and 100%, respectively. Overall median survival time was 393 days and the median survival time for dogs with OSA was 449 days.

Conclusion—Intercalary limb-sparing surgery results in better postoperative limb function with fewer and less severe complications than historical reports of dogs treated with non-intercalary limb-sparing surgery.

Clinical Relevance—In dogs with diaphyseal tumors, intercalary limb-sparing surgery preserves normal joint function and results in good to excellent limb use with few complications and good local tumor control.

Key words: intercalary bone graft, limb sparing, diaphyseal tumor, osteosarcoma, dog.

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INTRODUCTION

OSTEOSARCOMA (OSA) is the most common primary bone tumor of dogs.[1] Treatment of dogs with non-metastatic appendicular OSA involves surgical ablation of the primary tumor and postoperative chemotherapy. Surgical options for the management of the local tumor include limb amputation and limb-sparing techniques. Limb-sparing surgery frequently involves arthrodesis of the adjacent joint as most appendicular OSA are metaphyseal in location.[1–5] Diaphyseal OSA is rare and occurs in $<5\%$ of dogs with appendicular OSA.[5] Metastatic carcinomas (i.e., urinary transitional cell carcinoma, prostatic carcinoma, mammary carcinoma, and apocrine gland anal sac adenocarcinoma) are more common than primary sarcomas in this region and, as such, additional diagnostic tests that should be considered for dogs with diaphyseal lesions include rectal examination, abdominal ultrasonography, nuclear scintigraphy, and bone biopsy.[6] A principal advantage in the surgical management of diaphyseal tumors is that they are amenable to intercalary resection with subsequent preservation of both limb and joint function. In humans, limb salvage using intercalary resection is associated with fewer complications and better postoperative limb function than other limb-sparing techniques, such as allograft–arthrodesis, allograft–prosthesis, or endoprosthesis.[7–13]

Our purpose was to evaluate the efficacy and outcome of limb- and joint-sparing surgery in dogs using allografts or irradiated autografts for reconstruction of intercalary defects after resection of high-grade tumors of the diaphysis.

MATERIALS AND METHODS

The bone tumor database and medical records (January 1986–December 2002) at Colorado State University Veterinary Teaching Hospital were reviewed for dogs that had diaphyseal tumors treated with joint- and limb-sparing surgery using intercalary autografts or allografts. Dogs were excluded if limb-sparing surgery of the diaphyseal tumor involved arthrodesis of the adjacent joint.

Retrieved information included signalment, physical examination findings, blood test results, regional and 3-view thoracic radiographs, bone survey radiographs or nuclear scintigraphy, surgical findings and technique, histopathologic diagnosis, and postoperative outcome. Bone biopsy was either performed preoperatively or intraoperatively. Before 1995, bone survey radiographs, consisting of lateral radiographs of the limbs and ventrodorsal radiographs of pelvis and vertebral column, were performed to screen for metastatic disease to bone. Whole-body bone scans, using technetium^{99m} hydroxymethylene diphosphonate (Tc^{99m} HDP), were used to screen for skeletal metastases after 1995. 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.[14] These stages are then subdivided into A or B, depending on whether the local tumor is intra- or extracompartmental.[14]

The surgical approach and techniques were dependent on the anatomic site of the primary bone tumor and surgeon preference. Common to all dogs and regardless of the bone involved, en bloc resection of the tumor was performed including all contiguous soft tissue structures.[1–4] The affected bone was osteotomized a minimum of 2 cm proximal and distal to the tumor, as determined primarily by radiographic and scintigraphic imaging,[14,15] and secondarily by gross intraoperative examination. Bone marrow was collected from the medullary cavity opposite the osteotomized tumor segment and submitted for histopathologic evaluation of surgical margins. The diaphyseal defect was filled with either a massive cortical allograft or replacement of the resected bone after ex vivo extracorporeal irradiation.

In dogs reconstructed with cortical allografts, the allograft was selected from our institutional bone bank on the basis of the closest match in bone diameter as determined from preoperative radiographs. The allograft was thawed in a solution of sterile isotonic saline and gentamicin at room temperature and bone marrow was removed from the medullary cavity. The allograft was then cut to the appropriate length using an oscillating saw. For ex vivo irradiation, the resected segment of bone was placed in a sterilized zip lock bag filled with sterile saline 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 segment of bone was irradiated, using source-to-skin distance geometry, with a single 70 Gy fraction of 6 MV photons. The bone segment was returned to surgery and aseptically removed from the zip lock bag.

In some dogs, the medullary cavity was filled with tobramycin and vancomycin-impregnated polymethylmethacrylate (PMMA). The allograft or autograft was then fitted into the diaphyseal defect and stabilized using a dynamic compression plate (DCP), veterinary cuttable plate (VCP), interlocking nail (ILN), intramedullary pin, and/or orthopedic wire. A biodegradable implant containing 8% cisplatin [open-cell polylactic acid (OPLA-Pt), Kensey Nash Corporation, Exton, PA] was implanted into the surgical wound adjacent to the reconstructed bone in some dogs. A closed continuous suction drain was maintained at the surgery site for 12–24 hours postoperatively in all dogs and operated limbs were protected with soft-padded bandages for 3–5 days. Postoperative activity was restricted to leashed exercise for 4 weeks and then followed by unlimited exercise. Chemotherapy protocols involved single or dual agent therapy with cisplatin, doxorubicin, or carboplatin.

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. 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. Radiographs were evaluated for union of the graft–host bone interface. Non-union was defined as the presence of a radiographically visible osteotomy line >6 weeks after surgery.

Data Analysis

Limb use, surgical complications, local tumor recurrence, metastasis, and survival time were recorded. The percentage of dogs with an intact limb spare at the time of death or study end, 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 (MFI) were defined as the time from limb-sparing surgery to the detection of local tumor recurrence and distant metastasis, respectively. Survival time was defined as the time from surgery to either death or euthanasia.

Statistical Analysis

χ^2 was used to analyze the significance of associations between postoperative infection, implant failure, graft failure, and graft non-union with variables such as the bone and limb spared, use of PMMA and OPLA-Pt, and type of surgical fixation. Median MFI and survival time (MST) were calculated using Kaplan–Meier survival analysis with log rank. A P-value $<.05$ was considered significant.

RESULTS

Limb- and joint-sparing surgery was performed in 17 dogs with diaphyseal tumors using intercalary allografts or autografts.

Signalment

Breeds represented included 3 each of Dobermans, Rottweilers, and mix breed dogs; 2 each of Australian Shepherds and Golden Retrievers; and 1 each of an Alaskan Malamute, Labrador Retriever, German Shepherd, and Great Dane. Eight dogs were female (6 spayed) and 9 were male (8 neutered). Median age at admission was 10 years (range, 4–13 years) and median body weight was 34.1 kg (range, 22.7–53.4 kg). Reasons for admission included lameness (n = 4), visible mass (6), both lameness and mass (6), or other (1).

All dogs were staged with hematology, serum biochemistry, regional and 3-view thoracic radiographs, and either bone survey radiographs or nuclear scintigraphy (Figs 1 and 2). Hematologic abnormalities were non-specific and included mild anemia in 4 dogs and mature neutrophilia in 2 dogs. Alkaline phosphatase concentration was elevated in 6 dogs (range, 102–461 IU/L; reference range, 18–160 IU/L [5 dogs; alkaline phosphatase of 102 IU/L for 1 dog was within the current reference range but exceeded it when measured in 1987]).

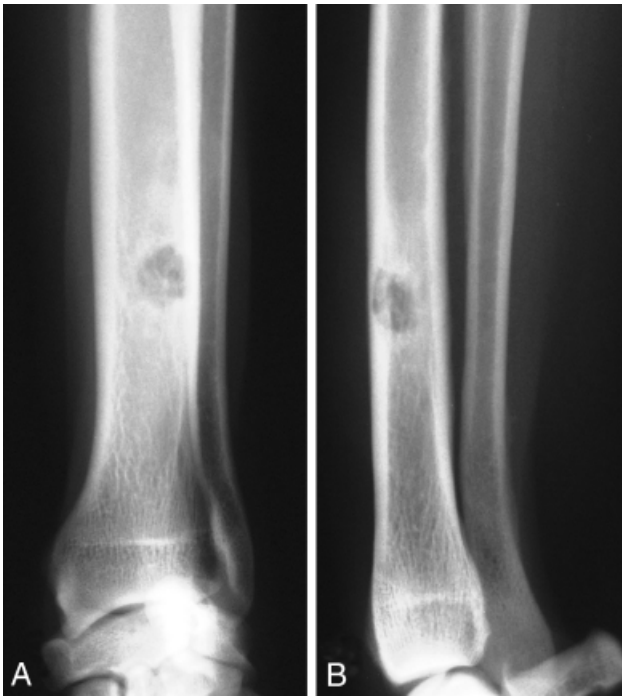

Fig 1. (A) Mediolateral and (B) dorsopalmar radiographs of a 10-year-old Australian Shepherd with a localized high-grade osteosarcoma of the distal diaphysis of the right radius.

Diagnostic Imaging

Radiographic changes typical of a bone tumor were seen in all affected limbs.[11] Bones involved were radius (n = 5), ulna (7), humerus (2), and tibia (3). Nine tumors were left sided and 8 were right sided. Thoracic radiographs were performed in all dogs. A single lung lesion was noted on thoracic radiographs in 1 dog and this was subsequently diagnosed as a primary myxosarcoma after lung lobectomy performed concurrently with limb-sparing surgery. Pulmonary metastasis was not evident in any dog. Bone biopsy was performed preoperatively in 9 dogs and was consistent with high-grade OSA in all dogs. Bone survey (n = 6) or whole-body nuclear scintigraphy (11) showed disease confined to the affected limb in all but 1 dog. In this dog, scintigraphic skeletal lesions were detected in both the mid-diaphysis of the tibia and distal metaphysis of the contralateral radius.

Surgery

The surgical approaches used were a dorsal approach to the radius, palmar approach to the ulna, medial

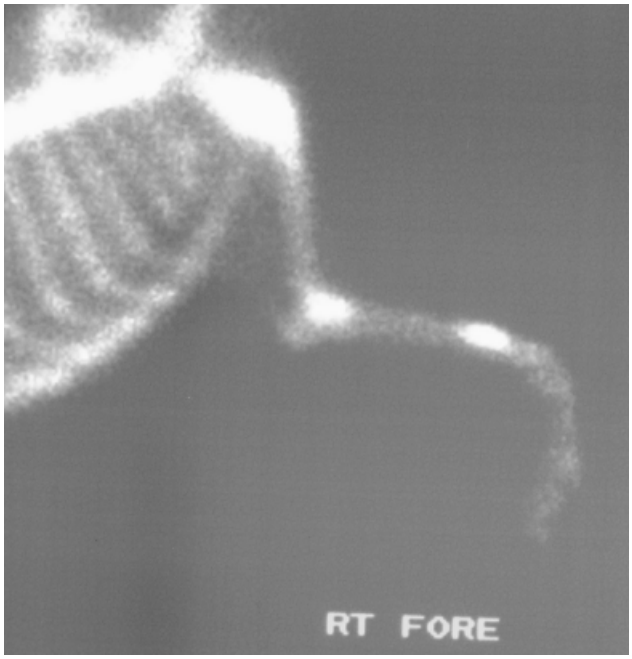

Fig 2. A delayed-phase technetium bone scan image of the dog in Fig 1. The distal diaphyseal osteosarcoma is localized to the radius. The tumor can be resected with a minimum of 2 cm margins beyond the scintigraphic limits of the tumor and antebrachiocarpal joint function can be preserved without compromising oncologic principles.

approach to the tibia, and lateral approach to the humerus. Resection of the bone tumor was performed in all cases with non-contiguous soft tissue dissected away from the tumor capsule. Soft tissue structures were resected en bloc with the bone tumor if adhered to the tumor capsule or invaded by the tumor (Fig 3A). Osteotomies were performed proximal and distal to the isolated bone tumor with a minimum of 2 cm margins, as determined by radiographic and scintigraphic imaging (Fig 3A).[15,16]

The diaphyseal defect was reconstructed using either a massive cortical allograft (n = 15) or ex vivo irradiated autograft (2; Fig 3B and C). The intramedullary cavity of the graft was filled with antibiotic-impregnated PMMA in 6 dogs with allografts and both dogs with autografts. Radial grafts were stabilized with a single 3.5 mm broad DCP (n = 3), 2 stacked 2.7/3.5 mm VCP (1; Figs 3D and 4A), and a single 3.5 mm broad DCP proximally with a 3.5 mm T-plate and 2 Rush pins distally (1). A variety of techniques were used to stabilize ulnar allografts, including a single intramedullary pin (n = 1), intramedullary pin combined with a pin and tension band wire distally (1), 2 proximal intramedullary pins and 1 distal intramedullary pin (1), single 2.7 mm DCP proximally and either 2 crossed K-wires or pin and tension band wire distally (2), and single 3.5 mm narrow DCP proximally and either a single 2.7 mm DCP or 2 stacked 2.0/2.7 mm VCP distally (2). Humeral allografts were stabilized using a lateral 3.5 mm broad DCP either alone (n = 1) or in combination with a cranial 2.7 mm DCP (1). A single 3.5 mm broad DCP (n = 2) or 8 mm ILN with 2 interlocking screws proximally and distally (1) were used to stabilize tibial grafts. In 1 dog with synchronous lesions in both the mid-tibia and contralateral distal radius, a second limb-sparing surgery was performed, simultaneously with intraoperative radiation therapy of the tibial lesion, by resection of the distal radial tumor and reconstruction with a cortical allograft and pancarpal arthrodesis. OPLA-Pt was implanted adjacent to the reconstructed diaphysis in 9 dogs with allografts and both dogs with irradiated autografts (Table 1).

Histopathology

Histopathologic evaluation of bone tumors confirmed high-grade malignancy in all dogs, including OSA (n = 15), histiocytic sarcoma (1), and metastatic pulmonary adenocarcinoma (1). Preoperative biopsy was performed in 9 dogs and these results correlated with the postoperative diagnosis in all dogs. According to the Enneking system for the staging of soft tissue and bone sarcomas, the 16 dogs with primary bone sarcomas were systemically staged with stage IIB (n = 15) or III (n = 1) disease.[14] Tumor resection was histologically complete in 11 dogs and incomplete in 6 dogs. Forequarter amputation was performed in 1 dog 4 days post limb sparing to prevent local tumor recurrence after incomplete resection of an OSA of the radial diaphysis. This dog was excluded from further analysis. Owners of the remaining dogs with incomplete resection declined limb amputation.

Antibiotic Administration

Postoperatively, 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 every 24 hours) or carprofen (2.2 mg/kg every 12–24 hours), for 10–21 days. First-generation cephalosporins were administered throughout the course of chemotherapy and continued for 4 weeks after completion of chemotherapy.

Chemotherapy

Chemotherapy was administered to 15 dogs. The owner of the dog with appendicular OSA and pulmonary myxosarcoma elected not to proceed with postoperative chemotherapy. One dog was administered 2 doses of intra-arterial cisplatin preoperatively in combination with 10 fractions of 2.8 Gy of radiation to a mid-diaphyseal

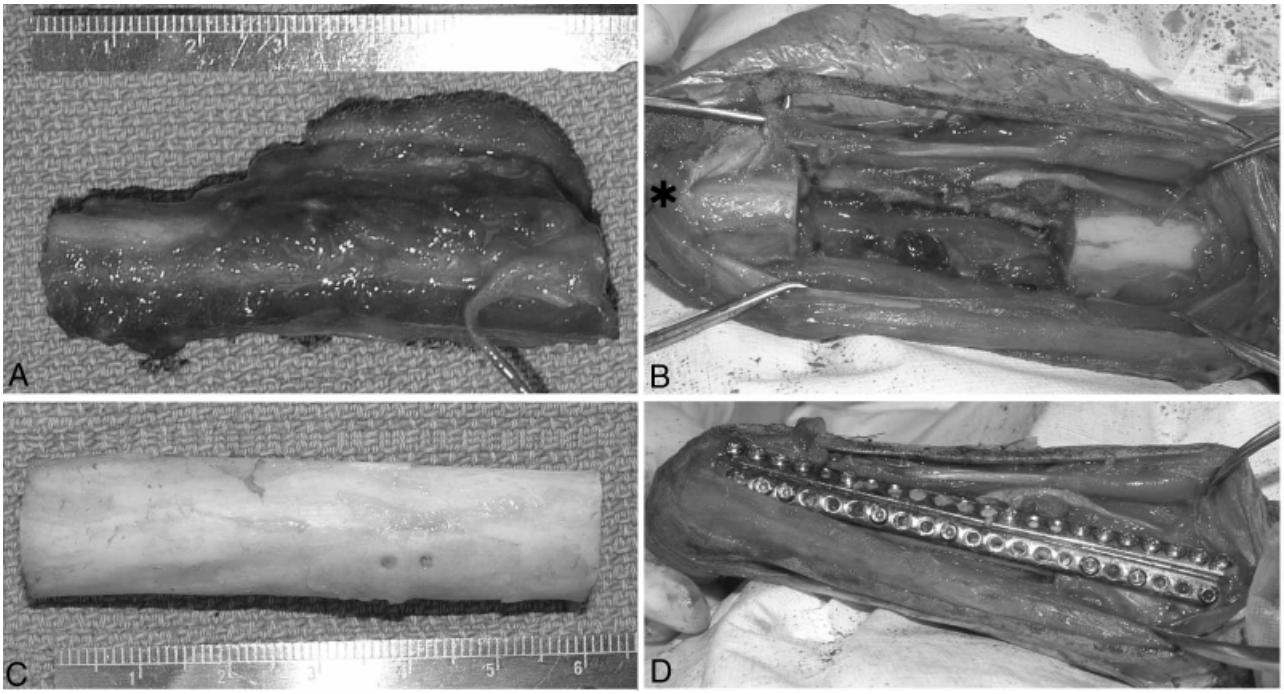

Fig 3. (A) The osteosarcoma lesion is resected with 2 cm margins and contiguous soft tissue structures; (B) after tumor resection, approximately 2 cm of the radius is preserved proximal to the antebrachiocarpal joint (*) to allow fixation of the intercalary graft; (C) the intercalary autograft is irradiated with a single fraction of 70 Gy and all irradiated soft tissue structures are removed from the autograft (2 biopsy tracts are noted at the tumor site); and (D) the segmental diaphyseal defect is reconstructed by filling the intercalary graft with bone cement and stabilizing the autograft with 2 stacked 2.0/2.7 mm veterinary cuttable plates.

ulnar OSA on a Monday–Wednesday–Friday protocol for a total dose of 28 Gy. The remaining 14 dogs were targeted to receive full-course, intravenous adjuvant chemotherapy, including 2–4 doses of cisplatin (70 mg/m^2 every 3 weeks) with concurrent saline diuresis (n = 7), 5 doses of doxorubicin (30 mg/m^2 every 3 weeks; 2 dogs), 4 doses of carboplatin (300 mg/m^2 every 3 weeks; 1 dog), or an alternating protocol of doxorubicin (30 mg/m^2) and either cisplatin (70 mg/m^2, 1 dog) or carboplatin (300 mg/m^2, 3 dogs) every 3 weeks for 6 treatments in total. One dog with stage III OSA at the time of diagnosis did not complete the targeted chemotherapy course as carboplatin was stopped when pulmonary metastasis was detected 99 days postoperatively.

Limb Function

Limb function was subjectively assessed at various time intervals ranging from 13 to 658 days postoperatively. Limb function was considered excellent in 8 dogs (50%) and good in the remaining 8 dogs (50%; Table 1).

Complications

Surgical complications occurred in 5 dogs (31.3%) with 4 dogs having a single complication and 1 dog having 3 complications. Infection was reported in 2 dogs (12.5%) at 201 and 417 days postoperatively. In both dogs, infection was superficial and controlled with oral antibiotic therapy. There was no significant relationship between infection and the use of OPLA-Pt, PMMA, implant or graft failure, or graft union.

Implant failure occurred in 4 dogs (25.0%) and included pin migration (n = 2), screw loosening (1), and plate loosening (1). An intramedullary pin was removed from 1 dog with proximal pin migration but no other case required revision and these dogs remained asymptomatic despite implant loosening. Implant failure was significantly associated with non-cemented allografts ($P = .042$) and implantation of intracavitary OPLA-Pt adjacent to the surgery site ($P = .009$). All implant failures occurred in the ulna and this relationship approached significance ($P = .077$). There was no significant association between implant failure and other variables such as the use of irradiated grafts ($P = .404$), type of fixation ($P = .801$), infection ($P = .383$), local recurrence ($P = .157$), and non-union ($P = .157$). In 1 dog with both infection and plate loosening, the distal aspect of the graft atrophied secondary to infection and fractured. Graft failure was significantly associated with postoperative infection ($P = .006$) but not any other examined variable. All these complications were late and occurred 76–411 days postoperatively (Table 1).

Follow-Up Radiographs

Radiographs or radiographic reports were available for evaluation of the graft–host bone union in 12 dogs. In 10 dogs (83.3%), 1 or both of the proximal and distal interfaces had not united after a median of 146 days postoperatively (range, 53–515 days; Fig 4B). Of these 12 dogs, union of the proximal graft–host interface was radiographically evident in 3 dogs, distal graft–host interface in 1 dog, and both the proximal and distal interfaces in 2 dogs. There was a significant association between non-union and the use of PMMA ($P = .046$), implantation of OPLA-Pt ($P = .046$), and intercalary grafting of the ulna ($P = .025$), and humerus ($P = .025$). Chemotherapy administration ($P = .070$) approached significance.

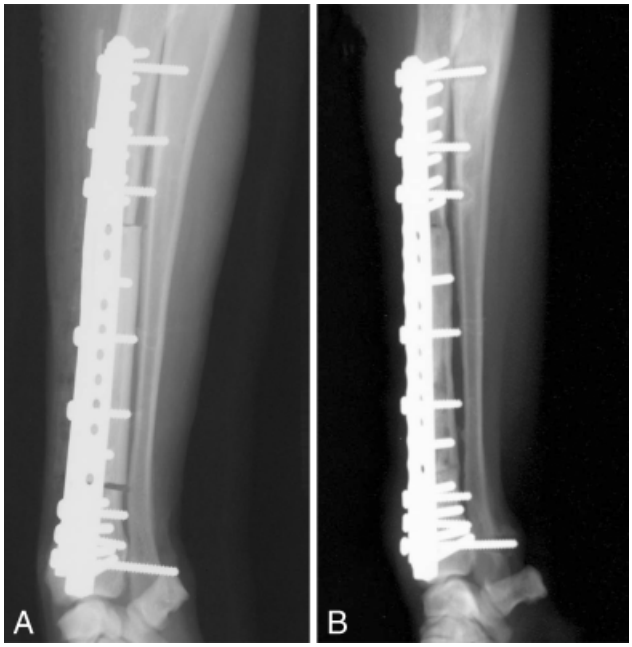

Fig 4. (A) Postoperative mediolateral radiographs illustrate good anatomic fit and adequate fixation of the intercalary autograft for the dog in Fig 1–3; (B) Non-union of both the proximal and distal osteotomies is radiographically visible 12 months postoperatively in the same dog. Non-unions, despite being frequently diagnosed, were not associated with clinical signs, and did not require surgical intervention.

Disease-Related Adverse Effects

Disease-related adverse effects were diagnosed in 12 dogs (75%). Local tumor recurrence was noted at necropsy in 1 dog (6.3%) without clinical signs, 117 days after incomplete resection of an ulnar diaphyseal OSA. The association between incomplete resection and local tumor recurrence approached significance ($P = .126$). OPLA-Pt did not significantly decrease the incidence of local tumor recurrence ($P = .242$) in these dogs. The disease-free and overall limb-salvage rate was 94% and 100%, respectively. Metastatic disease was diagnosed in 12 dogs (75.0%), with metastatic sites including the lungs alone (n = 5), bone alone (2), bone and lung (1), and multiple sites (4), such as the lungs, bone, heart, mediastinal lymph node, liver, adrenal glands, kidneys, spleen, and eye. The median MFI was 137 days (range, 6–682 days). Hypertrophic osteopathy secondary to

Table 1. Surgical Technique and Outcome in 17 Dogs with Diaphyseal Bone Tumors Treated with Intercalary Bone Grafts

Cases	Site	Graft Type	PMMA*	OPLA†	Surgical Technique	Infection	Implant Failure	Limb Function
1	Ulna	Allograft	No	No	Pin and K-wire	No	No	Excellent
2	Ulna	Allograft	No	Yes	Pins (2)	No	No	Excellent
3	Ulna	Allograft	No	No	DCP‡ and K-wire	No	Pin migration	Good
4	Ulna	Allograft	Yes	No	DCP and tension band wire	No	No	Excellent
5	Tibia	Allograft	Yes	Yes	DCP	No	No	Good
6	Ulna	Allograft	No	No	DCP and VCP§ (2)	Superficial	Plate loosening	Good
7	Humerus	Allograft	Yes	Yes	DCP	No	No	Excellent
8	Radius	Allograft	Yes	Yes	DCP	No	No	Good
9	Ulna	Allograft	No	No	DCP (2)	No	Screw breakage	Good
10	Humerus	Allograft	Yes	Yes	DCP (2)	No	No	Excellent
11	Radius	Allograft	No	No	DCP	No	No	Excellent
12	Radius	Allograft	Yes	Yes	DCP	NA¶	NA	NA
13	Radius	Allograft	No	Yes	DCP, T-plate and pins (2)	Superficial	No	Good
14	Tibia	Allograft	No	Yes	Interlocking nail	No	No	Excellent
15	Tibia	Autograft	Yes	Yes	DCP	No	No	Good
16	Radius	Autograft	Yes	Yes	VCP (2)	No	No	Excellent
17	Ulna	Allograft	No	No	Pin	No	Pin migration	Good

*PMMA, polymethylmethacrylate.
†OPLA, open cell polylactic acid containing cisplatin.
‡DCP, dynamic compression plate.
§VCP, veterinary cuttable plate.
¶NA, not assessable.

Table 2. Oncologic Outcome in 17 Dogs with Diaphyseal Bone Tumors Treated with Intercalary Bone Grafts

Case	Diagnosis	Adjunctive Treatment	Local Recurrence	Metastasis	MFI* (days)	Death	Survival Time (days)
1	OSA†	Cisplatin (2)	No	Bone	377	Metastasis	449
2	OSA	Radiation and cisplatin (2)	No	Multiple	6	Metastasis	178
3	OSA	Cisplatin–Doxorubicin (6)	No	Lungs	21	Metastasis	364
4	OSA	Cisplatin (3)	Yes	Lungs	109	Metastasis	117
5	OSA	None	No	Lungs	155	Metastasis	751
6	OSA	Cisplatin (4)	No	Bone, lungs	292	Metastasis	788
7	Metastatic ADC‡	Doxorubicin (5)	No	Multiple	137	Metastasis	190
8	Histiocytic sarcoma	Cisplatin (4)	No	Bone	22	Metastasis	288
9	OSA	Cisplatin (3)	No	Multiple	386	Metastasis	193
10	OSA	Cisplatin–carboplatin (2)	No	No	—	LTFU§	179
11	OSA	Cisplatin (4)	No	Lungs	862	Metastasis	682
12	OSA	NA¶	NA	NA	NA	NA	NA
13	OSA	Carboplatin–doxorubicin (4)	No	No	—	CNS disease	715
14	OSA	Carboplatin–doxorubicin (6)	No	Skin	340	Metastasis	393
15	OSA	Carboplatin (1)	No	Lungs	99	Metastasis	198
16	OSA	Carboplatin–doxorubicin (6)	No	No	—	Alive	552
17	OSA	Doxorubicin (5)	No	No	—	Unknown	369

*MFI, metastasis-free interval.
†OSA, osteosarcoma.
‡ADC, adenocarcinoma (pulmonary).
§LTFU, lost to follow-up.
¶NA, not assessable.

pulmonary metastasis was diagnosed in 1 dog 6 days postoperatively. These pulmonary lesions were not evident on preoperative 3-view thoracic radiographs. Pulmonary metastatectomy was performed and the dog was euthanatized 178 days after limb-sparing surgery because of metstatic disease. One dog was alive and disease-free 552 days postoperatively. Twelve dogs died or were euthanatized because of metastasis, 1 dog was lost to follow-up 179 days postoperatively, and 2 dogs died from unrelated causes (Table 2). The MST for dogs with OSA was 449 days (range, 117–788 days) whereas the overall MST for all tumor types was 393 days (range, 117–788 days).

DISCUSSION

Limb-sparing surgery is becoming more widely accepted and used in the management of dogs with appendicular OSA. Most primary bone tumors occur in the metaphyseal region of long bones and limb sparing in these cases usually necessitates arthrodesis of the adjacent joint.[1–5] In humans, joint-sparing procedures are preferred as limb salvage techniques involving arthrodesis are associated with a relatively high complication rate.[10,11] Limb- and joint-salvage techniques for tumors in the metaphyseal region include prostheses with and without allografting.[10,11] For diaphyseal lesions, intercalary resection and reconstruction preserve both joint and limb anatomy and function and, of all the different limb-sparing techniques in humans, is associated with the best postoperative results and functional outcome.[7–13]

In the present series, intercalary resection, with preservation of limb and joint function, was performed in 17 dogs with malignant diaphyseal tumors. Cortical allografts were used in 15 dogs and irradiated autografts in 2 dogs. Extracorporeally irradiated autografts provide a readily available source of cortical bone without the need for a bone bank and a good anatomic fit into the segmental diaphyseal defect. Furthermore, a single fraction of ≥ 50 Gy is tumoricidal and should prevent local tumor recurrence within the radiation field.[17,18] Other alternatives to cortical allografts for intercalary reconstruction in oncologic surgery include distraction osteogenesis and sterilization of autografts by autoclave or pasteurization.[19–23] The use of autografts may be contraindicated in dogs with primarily lytic tumors as the structural integrity of the cortical bone is further weakened by the sterilization process and this may predispose to graft and limb-salvage failure.[17–21]

Limb function was assessed as good to excellent in all 16 dogs available for postoperative analysis. This evaluation was limited by the subjective criteria used for assessing the degree and duration of lameness and the retrospective design of this study. However, the functional outcome after intercalary limb-sparing surgery is better than historical reports of allograft–arthrodesis of the distal radius in which good to excellent limb function is

reported in 69–90% of dogs.[1–3] Furthermore, 5 of the diaphyseal tumors were located in either the humerus or tibia. Allograft–arthrodesis in both of these bones is associated with poor postoperative limb function.[1–4] In humans, intercalary resection results in the best limb function of all the limb-sparing techniques, with function rated as good to excellent in 84–100% of cases, while only 54–59% of allograft–arthrodesis limb salvages result in good to excellent function.[7–13] The improvement in functional outcome after intercalary resection is most likely because of preservation of normal joint anatomy and function as arthrodesis alters gait kinetics and limb function.[24]

The postoperative complication rate in these dogs was 31%. Infection is often cited as the most common and serious complication after limb-sparing surgery.[1,2,10,11,13,25,26] An infection rate of 30–70% has been reported after allograft–arthrodesis of the distal radius in dogs.[1–4,25,26] Furthermore, these infections are often deep and refractory to management with culture-directed antibiotics and implantation of antibiotic-impregnated PMMA beads.[25] In contrast, the infection rate in the present study was only 13% and both dogs had superficial infections that were responsive to appropriate antimicrobial therapy. The pathophysiology of post-limb-sparing infection is unknown although hypotheses include extensive soft tissue resection, poor soft tissue coverage, implantation of orthopedic implants and non-vascularized cortical bone, and administration of local and systemic chemotherapy.[13,25] The incidence and severity of infection may have been lower in the present series as intercalary reconstructions were performed in regions with greater soft tissue coverage than the distal extremities resulting in better vascularization and greater resistance to infection.[8,13]

Implant failure was the most common complication (25%) and only occurred in the ulna. The proximal and distal ulnar osteotomies were often stabilized separately and human studies have shown that this method of fixation is more prone to failure than a single implant spanning both allograft–host bone interfaces.[12] Furthermore, most ulnar allografts were stabilized with less rigid implants, such as intramedullary pins, and the resultant micromotion and instability may have contributed to implant loosening.[27] A similar rate of implant complications has been reported after stabilization of olecranon osteotomies.[28] Lastly, and perhaps most importantly, implant failure was associated with non-cemented intercalary grafts. Intramedullary PMMA has been shown to significantly reduce the rate of implant and allograft failure after limb-sparing surgery in both dogs and humans.[26,29,30] Regardless, in the present series, most implant failures involved asymptomatic pin and screw loosening and none resulted in catastrophic failure or required major revision. Moreover, most ulnar intercalary limb-sparing surgeries were performed before 1994 and it has since been shown that excellent limb function can be preserved in dogs with ulnar OSA by tumor resection without subsequent osseous reconstruction.[31]

Non-union of 1 or both osteotomies was diagnosed in 83% of dogs a minimum of 53 days postoperatively (median, 146 days; range, 53–515 days). Non-union is a subjective assessment and the definition of 6 weeks we used may be overly strict as allograft incorporation is a slower and more protracted process than normal bone healing.[32] We found a significant association between non-union and the use of OPLA-Pt and PMMA. Cisplatin released from OPLA-Pt is cytotoxic and significantly reduces the risk of local tumor recurrence.[33] However, cisplatin-induced cytotoxicity is non-specific and may also adversely affect revascularization and other cellular events involved in normal bone healing. Systemic chemotherapy has a similar cytotoxic effect and delays healing and significantly increases the rate of allograft non-union.[29,34–37] Chemotherapy reduces the rate and quality of bone healing in a dose-dependent manner through cytotoxic effects on osteoblasts, osteoclasts, and endothelial cells.[29,34,35] Locally released chemotherapy results in a significantly higher local drug concentration than the same agent administered systemically and hence it is likely that the cytotoxic effects of OPLA-Pt are greater than systemic cisplatin.[38] Intramedullary PMMA has been reported not to adversely affect bone healing and allograft incorporation in a canine intercalary allograft model.[39] In contrast to these findings, our results support other human reports where the rate of non-union is higher in cemented than non-cemented intercalary allografts.[29,40] The effect of PMMA on allograft healing may be minimized by recessing the PMMA below the level of the proximal and distal extents of the allograft and filling the resultant gap with cancellous bone graft.[40] A significantly higher incidence of non-union was associated with intercalary reconstruction of the ulna and humerus compared with other appendicular sites. Ulnar non-unions were most likely caused by the high rate of implant failure while the 2 dogs treated with humeral limb-sparing surgery were evaluated at 53 and 137 days postoperatively and this may have been insufficient for the assessment of nonunion. In humans, intercalary allograft reconstruction is also associated with a higher rate of non-union than other limb-sparing techniques as diaphyseal osteotomies have a slower rate of healing than osteotomies in metaphyseal bone.[8,12,13,37,40,41] The effect of non-union on graft survival and limb salvage is conflicting with both negligible[10,12,40] and negative impacts reported.[8,36,37] In the present series, non-union of the allograft–host bone interface was a radiographic finding

only and not associated with clinical signs, and as a result, did not require surgical intervention.

Disease-related adverse events were diagnosed in 75% of dogs. Local tumor recurrence was diagnosed in 1 dog with an ulnar OSA, which is lower than expected considering that resection was incomplete in 5 dogs. However, in 3 of these dogs, OPLA-Pt was implanted adjacent to the surgery site and this has been shown to significantly reduce the rate of local tumor recurrence in dogs with distal radial OSA.[33] Intracavitary OPLA-Pt was not used in the 1 dog with local tumor recurrence. The ability to achieve complete osseous resection of the tumor improved after 1995 when nuclear scintigraphy was introduced as Tc^{99m} HDP bone scans overestimate the degree of bone involvement and increase the likelihood of complete surgical resection when osteotomies are planned on the basis of these findings.[15,16] Furthermore, we used a minimum of 2 cm margins for intercalary resection and, because of the high incidence of incomplete excision, this may be insufficient for resection of osseous tumors. Gross surgical margins could not be assessed because of the retrospective design of this study, however, a minimum of 3 cm margins should be considered for future cases of intercalary limb-sparing surgery. Distant metastatic disease was diagnosed in 12 dogs, including both dogs with non-OSA diaphyseal tumors, with a median MFI of 137 days. The MST of 449 days for dogs with diaphyseal OSA treated with intercalary limb-sparing surgery and, in all but 1 dog, adjuvant chemotherapy is numerically superior to historical reports of 235–366 days for dogs managed with limb amputation or salvage and postoperative chemotherapy.[2–4,42–51] The prognosis for dogs with diaphyseal OSA may be better than metaphyseal sites, similar to dogs with OSA distal to the carpus and tarsus,[52] although this is difficult to conclude based on the small sample population and difficulty in comparing results with other retrospective studies. Regardless, diaphyseal OSA remains an aggressive tumor with a high metastatic rate.

Intercalary resection and reconstruction is recommended for salvage of limb and joint function in dogs with diaphyseal tumors in non-ulnar sites. In dogs with tumors of the ulna, reconstruction is not recommended because of a high complication rate and good postoperative limb function after intercalary resection without reconstruction.[31] Intercalary resection and preservation of joint function should not be performed if preoperative nuclear scintigraphy suggests that a minimum of 3 cm margins cannot be achieved without compromising surgical margins. The injection of PMMA into the medullary cavity of the allograft is recommended to minimize the risk of implant failure and, if available, intracavitary OPLA-Pt should be considered for local tumor control.[33] Non-union of 1 or both osteotomies was frequently diagnosed but clinically insignificant. The disease-free and overall limb-salvage rate was 94% and 100%, respectively, with a MST of 449 days for dogs with diaphyseal OSA.

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