

# Cortical Allograft and Endoprosthesis for Limb-Sparing Surgery in Dogs with Distal Radial Osteosarcoma: A Prospective Clinical Comparison of Two Different Limb-Sparing Techniques

JULIUS M. LIPTAK, BVSc, MVCS, FACVSc, Diplomate ACVS & ECVS, WILLIAM S. DERNELL, DVM, MS, Diplomate ACVS, NICOLE EHRHART, VMD, MS, Diplomate ACVS, MARY H. LAFFERTY, CVT, GABRIELLE J. MONTEITH, BSc, and STEPHEN J. WITHROW, DVM, Diplomate ACVS & ACVIM (Oncology)

**Objective**—To compare surgical and oncologic outcome in dogs with osteosarcoma (OSA) of the distal aspect of the radius treated with limb-sparing surgery, using either a cortical allograft or endoprosthesis, and postoperative chemotherapy; and to evaluate predictive factors for outcome.

**Study Design**—Prospective cohort study.

**Animals**—Dogs (n = 20) with spontaneous, non-metastatic OSA of the distal aspect of the radius.

**Methods**—Dogs were prospectively randomized for limb-sparing surgery with either a cortical allograft (n = 10) or endoprosthesis (10) and full-course adjuvant chemotherapy using single or dual agent protocols of cisplatin, carboplatin, and/or doxorubicin. Surgical (intraoperative findings, postoperative infection, construct failure) and oncologic (local tumor recurrence, metastasis, survival) outcomes were compared. The influence of intraoperative and postoperative variables on surgical and oncologic outcome were evaluated.

**Results**—No clinically significant differences in surgical and oncologic outcome were detected between groups. The percentage of radius replaced by the implant was significantly greater in the endoprosthesis group (60.9% compared with 48.6%,  $P = .008$ ). Median survival time (MST) for dogs with construct failure, regardless of implant type, was 685 days and significantly greater than MST of dogs without construct failure (322 days,  $P = .042$ ; hazard ratio [HR] 16.82). Median metastasis-free interval and MST (685 days versus 289 days;  $P = .034$ , HR 24.58) were significantly greater in dogs with postoperative infection. Disease-free and overall limb-salvage rates were 70% and 85%, respectively. Overall MST was 430 days.

**Conclusions**—For dogs with OSA of the distal aspect of the radius, a cortical allograft or endoprosthesis can be used for limb-sparing surgery. Construct failure and postoperative infection significantly improve survival time regardless of implant type.

**Clinical Relevance**—An endoprosthesis is an attractive alternative to cortical allografts for limb-salvage of the distal aspect of the radius in dogs because surgical and oncologic outcomes are similar, but the endoprosthesis is an immediately available off-the-shelf implant which is not complicated by the bone harvesting and banking requirements associated with cortical allografts. Mechanisms whereby postoperative infection improves survival time requires further investigation and, if elucidated, may provide the opportunity to improve the outcome of dogs and humans with OSA.

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From the Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO; and Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada.

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Dr. Liptak's present address is Alta Vista Animal Hospital, 2616 Bank Street, Ottawa, ON, Canada K1T 1M9.

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## INTRODUCTION

**O**STEOSARCOMA (OSA) is the most common primary bone tumor of the canine skeleton.<sup>1</sup> In dogs, OSA has a predilection for the metaphyseal region of the appendicular skeleton of middle-aged, large breed dogs, and the distal aspect of the radius is the most commonly affected site.<sup>1</sup> The gold standard curative-intent treatment for dogs with appendicular OSA involves limb amputation for control of the local tumor and adjuvant chemotherapy for management of metastatic disease.<sup>1,2</sup> Limb-sparing surgery has become the standard of care in humans with primary bone tumors and is a viable alternative to limb amputation in dogs, especially if concomitant conditions exist that are relative or absolute contraindications for limb amputation, such as neurologic disease or debilitating osteoarthritis, or if owners are reluctant to proceed with limb amputation.<sup>1,2</sup> Limb-sparing surgery involves resection of the tumor and reconstruction of the bony column, with or without arthrodesis of the adjacent joint.<sup>1,2</sup> Limb-salvage procedures have been described in the distal aspect of the radius,<sup>3-8</sup> proximal humerus,<sup>9,10</sup> distal tibia,<sup>3,10,11</sup> and proximal femur<sup>12</sup> in dogs with OSA, but limb-sparing surgery for tumors of the distal aspect of the radius has produced the most favorable results.<sup>3-6</sup> This is largely because pancarpal arthrodesis is well tolerated by dogs,<sup>13-15</sup> whereas arthrodesis of other sites (e.g., shoulder, stifle, and tarsus) is associated with poor postoperative limb function.<sup>3,9</sup>

Cortical allografts (CAs) have traditionally been used to reconstruct the radius after tumor resection.<sup>1-6</sup> The use of massive CAs is associated with a high complication rate in both human and veterinary patients, including infection, construct failure, and tumor recurrence.<sup>1-6,16-22</sup> As a result, surgeons have been investigating alternative methods of reconstructing the bone defect in an attempt to decrease the complication rate, especially infection and implant failure. Reported techniques include distraction osteogenesis using circular fixators,<sup>7,8,11</sup> and vascularized,<sup>23</sup> irradiated,<sup>10</sup> and pasteurized autografts.<sup>24</sup> Most of these techniques are limited by surgical training and expertise (e.g., distraction osteogenesis and vascularized autografts), access to specialized equipment and facilities (e.g., vascularized and irradiated autografts), and surgeon experience.

A 316L surgical steel endoprosthesis (EN) has recently become commercially available for limb-sparing surgery in the distal aspect of the radius of dogs (Veterinary Orthopedic Implants, Burlington, VT). This first-generation EN consists of a solid 122 mm segment of surgical steel with a flared distal end to abut the radial carpal bone and 2 machined screw holes at the distal and proximal ends to secure the dedicated limb-sparing plate (Fig 1). The 24-hole limb-sparing plate (Veterinary Orthopedic



**Fig 1.** The endoprosthesis and dedicated limb-sparing bone plate available for distal radial limb-sparing in dogs. (A) Disassembled view; (B) assembled view, top; (C) assembled view, side. Note the flared distal end of the endoprosthesis (arrow).

Implants) has a greater cross-sectional area than either a 3.5 mm broad or 4.5 mm narrow dynamic compression plates, round rather than oval screw holes to increase the amount of surgical steel per unit length of plate, screw hole diameters for the proximal aspect of the radius and radial carpal bone which accommodate 3.5 and 4.5 mm cortical bone screws and 4.0 mm cancellous bone screws, and a tapered distal end for the metacarpus with screw holes accommodating either 2.7 or 3.5 mm cortical bone screws. A comparison with the biomechanical properties of limbs reconstructed with either an EN or cortical bone graft in acute axial loading showed that the EN was significantly stronger and up to 33% stiffer than cortical bone grafts.<sup>22</sup> The potential advantages of an EN for the reconstruction of bone defects in limb-sparing surgery include a readily available implant with no need for special equipment, bone banking facilities, or external beam radiation therapy machines. Furthermore, the superior biomechanical properties of EN-reconstructed limbs may decrease the rate of construct failure<sup>22</sup> and the implantation of a biologically inert material may decrease the incidence and severity of postoperative infection commonly encountered in CA limb-sparing surgery by avoiding allogeneically-induced foreign body reactions.<sup>25-27</sup>

Our purpose was to compare surgical and oncologic outcomes of dogs with OSA of the distal aspect of the radius treated with limb-sparing surgery using either an EN or CA and full-course adjunctive chemotherapy. Our secondary aim was to identify factors which may influence surgical and oncologic outcome. We hypothesized that limb-sparing surgery of the distal aspect of the radius with an EN would result in a similar to superior surgical outcome compared with CAs, but that there would be no difference in oncologic outcome.

## MATERIALS AND METHODS

### Study Design

Dogs with spontaneously occurring, non-metastatic OSA of the distal aspect of the radius ( $n = 20$ ) were prospectively and randomly assigned to have limb-sparing surgery with either EN or CA. Owners requested limb-sparing surgery for treatment of the primary bone tumor and consented to inclusion of their dog in the study after a discussion of CAs and the potential advantages and disadvantages of ENs in limb-sparing surgery.

### Inclusion Criteria

Diagnostic tests performed before surgery included hematology, serum biochemistry, regional limb radiographs, 3-view thoracic radiographs to screen for pulmonary metastases, and nuclear scintigraphy using technetium<sup>99m</sup> hydroxymethylene diphosphonate (Oxidronate, Mallinckrodt Inc., St. Louis, MO) to screen for skeletal metastases and determine surgical margins.<sup>1,28-30</sup> Dogs were included in the study if there was no evidence of metastatic lesions on either thoracic radiographs or whole-body bone scintigraphy.

### Limb-Sparing Surgical Technique

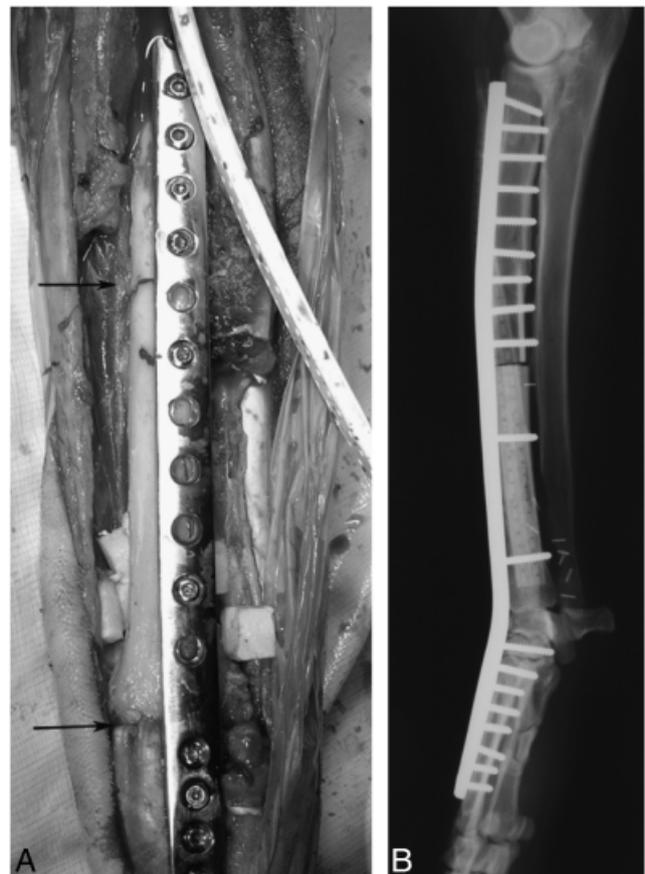
Limb-sparing was performed through a cranial or cranio-lateral approach to the radius. The bone tumor was resected en bloc with all contiguous tissue, including soft tissue structures and the biopsy tract if present. The ulna was also resected en bloc if there was radiographic, scintigraphic, or gross evidence of tumor extension from the radius into the ulna. The radius was osteotomized a minimum of 3 cm proximal to the tumor, as determined primarily by radiographic and scintigraphic imaging and secondarily by gross intraoperative examination.<sup>30</sup> A minimum of 3 cm surgical margins were used for limbs reconstructed with a CA; however, surgical margins were  $>3$  cm in limbs reconstructed with an EN as the EN is only available in a 122 mm length. The radius was disarticulated at the antebrachio-carpal joint and, if there was no evidence of secondary ulnar involvement, from the styloid process of the ulna. Bone marrow was collected from the proximal radial segment for histopathologic evaluation of surgical margins. The proximal aspect of the radial carpal bone was osteotomized with an oscillating saw to provide a flat surface to abut the distal end of either the CA or EN. The radial defect was then reconstructed with either a massive CA or EN. Dogs were randomly assigned to either the CA or EN group based on a coin flip.

For CA limb reconstruction, the CA was selected from our institutional bone bank on the basis of same side (i.e., right or left) and closest match in bone diameter as determined from preoperative limb radiographs and archival radiographs of the banked allograft. The CA was thawed in a 1L solution of sterile isotonic saline containing 1000 mg neomycin, 3000 mg ampicillin, and 500,000 U polymyxin B at room temperature and bone marrow was removed from the medullary cavity. The distal articular surface of the CA was osteotomized and

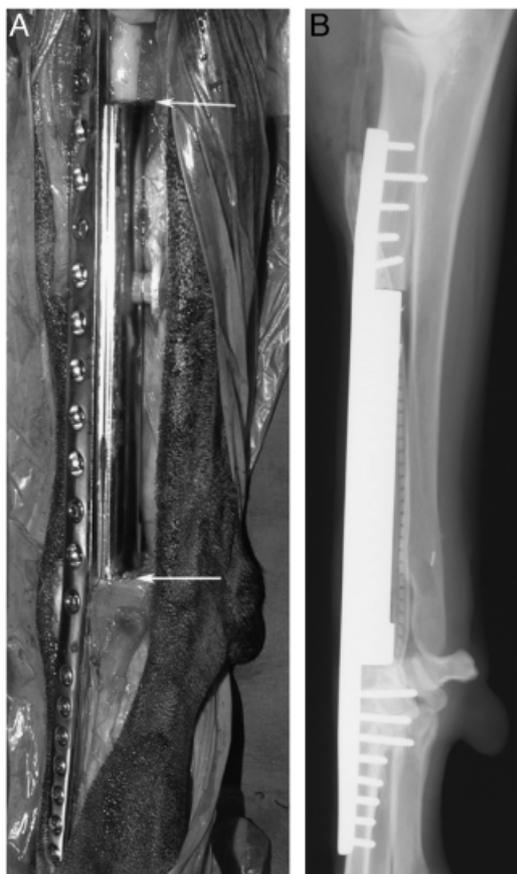
the allograft was then cut to the appropriate length using an oscillating saw, taking care to ensure maximal congruency at the interface between the allograft and host bone.

The dedicated limb-sparing bone plate was temporarily fixed to the CA with 2 cortical bone screws, 1 distal and 1 proximal. The bone screws were removed and the medullary cavity of the CA was filled with amikacin (1 g) impregnated polymethylmethacrylate (PMMA) in accordance with current limb-sparing recommendations.<sup>1,2,5</sup> As the PMMA started to harden, the cortical bone screws were reinserted to secure the limb-sparing bone plate to the CA. For limbs reconstructed with an EN, the dedicated limb-sparing bone plate was similarly secured to the EN with 2 EN-specific screws.

The distal radial defect was then filled with either the cemented CA (Fig 2) or EN (Fig 3) and the limb-sparing plate was fixed to the radius proximally and the radial carpal bone and third metacarpal bone distally using AO/ASIF techniques.<sup>31</sup> The bone plate was applied either straight or pre-bent to 10–15° depending on surgeon preference. A minimum of five 3.5 or 4.5 mm cortical bone screws were used in the



**Fig 2.** (A) Intraoperative image and (B) postoperative lateral radiograph of limb-sparing surgery of the distal aspect of the radius using a cortical allograft. Arrows depict proximal and distal extents of the cortical allograft (A). Biodegradable cisplatin-impregnated open-cell polylactic acid is implanted adjacent to the tumor resection site and a closed continuous suction drain is seen in the proximal aspect of the operative site.



**Fig 3.** (A) Intraoperative image and (B) postoperative lateral radiograph of limb-sparing surgery of the distal aspect of the radius using an endoprosthesis. Arrows depict the proximal and distal endoprosthesis–bone interfaces (A). Note the relatively long length of the endoprosthesis in comparison with the length of the radius and the length of the cortical allograft in Fig 2A. The percentage of radius replaced in limbs reconstructed with an endoprosthesis was significantly greater than limbs reconstructed with a cortical allograft (60.9% compared with 48.6%).

proximal radial segment and five 2.7 or 3.5 mm cortical bone screws were used in the radial carpal and third metacarpal bones. A minimum of 50% of the length of the third metacarpus was covered by the bone plate.

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 radius in all dogs. A closed continuous suction drain was maintained in the surgery site for 12–24 hours postoperatively and the 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, carboplatin, and/or doxorubicin,<sup>32–41</sup> depending on owner preference, and was started 10–14 days after limb-sparing surgery. Cephalexin was administered to all dogs from surgery until 4 weeks after the last dose of chemotherapy.

### *Surgical Outcome*

Evaluation of limb function, surgical infection, and construct failure was recommended monthly for the first 3 months, then every 3 months for 12 months, and every 6 months thereafter. Surgical infection was defined as the presence of  $\geq 1$  draining sinus tracts at the surgery site. If present, the time from surgery to first detection of infection, microbial culture results, and treatment methods were recorded. The severity of infection was graded as mild, moderate, or severe depending on response to oral antibiotics. A mild surgical infection was defined as draining sinus tracts that resolved after oral antibiotic therapy. A moderate surgical infection was defined as draining sinus tracts that responded to oral antibiotics but did not resolve. A severe surgical infection was refractory to oral antibiotic therapy. For infections that resolved with antibiotic administration (i.e., mild infections), therapy was continued for 1–2 weeks after clinical resolution of the draining tracts. Antibiotics were continued until either limb amputation or death for dogs with moderate and severe infections.

Construct failure was defined as loosening or breakage of either bone screws or bone plate, or fracture of the radius, CA or EN, or metacarpus. If present, the time from surgery to construct failure, type of construct failure, and treatment methods were recorded. Construct failure was graded as mild, moderate, or severe depending on the treatment method required to correct the construct failure. Mild failure was defined as a construct-related problem which did not require surgical revision, such as screw loosening or metacarpal fracture. Moderate failure was defined as a construct-related problem requiring minor surgical revision, such as removing, tightening, or replacing loosened bone screws. The decision on how to manage loosened or broken screws, and hence whether construct failure was defined as mild or moderate, was clinician dependent. Severe failure was defined as a construct-related problem requiring major surgical revision, such as bone plate replacement or limb amputation.

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.

### *Oncologic Outcome*

Regional limb and 3-view thoracic radiographs were recommended at the mid-point and end of chemotherapy, then every 3 months for 12 months, and every 6 months thereafter to screen for local tumor recurrence and pulmonary metastasis. Follow-up time was a minimum of 3 years or until death or euthanasia. Local tumor recurrence, metastasis, cause of death, and survival time were recorded. Local 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. Death was defined as tumor-related if death or euthanasia was because of local tumor recurrence or metastatic disease. Death was not considered tumor-related if the reason for death or euthanasia was non-neoplastic disease or a tumor other than OSA.

### Statistical Analysis

To assess if data was normally distributed between the CA and EN groups, a pooled Student t-test was used for age and a Satterthwaite t-test was used for body weight because variances were not equal between groups for weight. Total serum alkaline phosphatase (ALP) was increased in only 1 dog and hence there was no variation between groups for ALP.

The CA and EN groups were compared to assess whether there were any differences in surgical and oncologic outcome between the 2 groups. Student t-tests were used to compare intraoperative variables, such as surgery time, percentage of radius replacement by the implant, and percentage of metacarpal coverage by the limb-sparing plate, after determining they were normally distributed with equal variance as determined by a Shapiro–Wilk test and examination of residuals. Fisher's exact test was used to compare bending of the bone plate at the implant-radiocarpal bone junction, infection, construct failure, and local tumor recurrence. Wilcoxon Mann–Whitney t-tests were used to compare medians for proximal and distal screw number, severity of infection, severity of construct failure, and limb function. Surgical and oncologic factors were assessed using a Cox Proportional Hazards model for multivariate analysis and log-rank for univariate analysis.

Predictors of infection, construct failure, and local tumor recurrence were examined using univariate logistic regression and Fisher's exact test. Surgery time, en bloc resection of the ulna, percentage of radius replaced by the implant, and construct failure were examined as predictors of postoperative infection. Surgery time, en bloc resection of the ulna, bending of the bone plate at the implant-radiocarpal bone junction, percentage of radius replaced by the implant, proximal and distal screw number, percentage of metacarpal coverage by the bone plate, and infection were examined as predictors of construct failure. Preservation of the ulna was examined as a predictor of local tumor recurrence. Cox Proportional Hazards and log-rank were used to evaluate whether the percentage of radius replaced by the implant, postoperative infection, and construct failure predicted MFI or survival time.

Median MFI and survival time (MST) were calculated for the CA and EN groups and overall using Kaplan–Meier survival analysis with log-rank. Dogs were censored from survival analysis if either lost-to-follow-up or death was not tumor-related. A *P*-value of  $<.05$  was considered significant. Post-hoc power analysis was performed for all statistically non-significant results.

## RESULTS

### Signalment

Signalment was typical for dogs with appendicular OSA.<sup>1,28</sup> Median age and body weight for CA dogs were

8.3 years (mean, 8.0 years; range, 4.5–11 years) and 48.4 kg (mean, 51.6 kg; range; 29.5–79.5 kg), respectively. Median age and body weight for EN dogs was 8.3 years (mean, 8.2 years; range, 5.5–10 years) and 41.9 kg (mean, 44.8 kg; range, 35.2–62.7 kg), respectively. Total serum ALP concentrations were within the normal reference interval in all but 1 dog in the EN group. Data was distributed normally between the CA and EN groups (Table 1).

### Limb-Sparing Surgery

Limb-sparing surgery was performed without complication in all dogs. Median surgical time was not significantly different between groups: EN, 155 minutes (range, 120–180 minutes) and CA, 170 min (range, 125–211 minutes). Of all surgical variables, only the percentage of radius replaced by the implant was significantly different being greater in the EN group (median 60.9%) than the CA group (median 48.6%, *P* = .008, power = 0.96; Table 1). OSA were resected with complete histologic margins in all dogs.

Postoperative recovery was complicated in 1 dog in the CA group. In this dog, avascular necrosis of all digits on the operated limb necessitated limb amputation 13 days after limb-sparing surgery. The cause of avascular necrosis was not determined. Surgical resection of the tumor was typical and involved ligation and transection of the caudal interosseous artery and deep palmar arch of the common interosseous artery, and preservation of the cranial superficial antebrachial, radial, and superficial palmar arch of the median arteries. Hence, necrosis secondary to vascular ligation seems unlikely. Thrombosis of the preserved arterial supply and venous drainage was considered the probable cause for avascular necrosis of the digits. Thrombosis may have been caused by surgical manipulation or secondary to a localized intravascular coagulation, but systemic hypercoagulable diseases were not identified in this dog. Because this dog satisfied the inclusion criteria, it was not excluded from further analysis. Immediate postoperative recovery was uneventful in the remaining dogs in both groups.

### Postoperative Chemotherapy

After limb-sparing surgery, all dogs were administered curative-intent chemotherapy. Chemotherapy protocols included 4 doses of carboplatin (300 mg/m<sup>2</sup> every 3 weeks; CA group, *n* = 2; EN group, *n* = 2), 5 doses of doxorubicin (30 mg/m<sup>2</sup> every 3 weeks; CA group, *n* = 1; EN group, *n* = 2), or an alternating course of doxorubicin (30 mg/m<sup>2</sup>) and carboplatin (300 mg/m<sup>2</sup>; CA group, *n* = 7; EN group, *n* = 5) or cisplatin (70 mg/m<sup>2</sup>; EN group, *n* = 1) every 3 weeks for 6 treatments in total. In the CA group, 1 dog administered an alternating protocol of doxorubicin and carboplatin received an additional dose of

Table 1. Comparison of limb-sparing surgery with cortical allograft and endoprosthesis

Category	Cortical Allograft	Endoprosthesis	P-value	Power
Age	8.0 years	8.2 years	.869	0.050
Weight	48.4 kg	41.9 kg	.335	0.150
Serum total alkaline phosphatase	80 U/L	79 U/L	1.000	0.000
Surgery time	170 minutes	155 minutes	.184	0.250
Ulna preservation	80%	70%	1.000	0.031
Plate bending at implant-carpal junction	70%	40%	.370	0.075
Percentage of radius replaced by implant	48.6%	60.9%	.008*	0.960
Proximal screw number	7.5	5.5	.539	0.091
Distal screw number	8.0	8.0	.883	0.083
Percentage of metacarpus coverage	69.1%	78.3%	.346	0.150
Infection rate	60%	50%	1.000	0.012
Severity of infection	Severe	Severe	.917	0.055
Median time to infection	80 days	61 days	.443	0.119
Construct failure rate	40%	40%	1.000	0.012
Severity of construct failure	Moderate	Moderate	.455	0.050
Median time to construct failure	309 days	180 days	.324	0.166
Limb function	Mild lameness	Mild lameness	.968	0.077
Local tumor recurrence	10%	20%	1.000	0.049
Metastasis	80%	60%	.629	0.076
Metastasis-free interval	336 days	188 days	.951	0.050
Survival time	412 days	705 days	.146	0.440

\*significant result. Note that all numerical data is expressed as a median and all categorical data is expressed as a mode.

each chemotherapy agent, resulting in a total of 8 treatments. In the EN group, 2 dogs were started with a single dose of cisplatin but, because of cisplatin-associated toxicity (gastrointestinal toxicity [n = 1] and nausea and increased creatinine level [n = 1]), changed to and completed single-agent doxorubicin (n = 1) or carboplatin (n = 1) protocols; 1 dog treated with an alternating protocol of doxorubicin and cisplatin was administered an additional dose of each chemotherapy agent, resulting in a total of 8 treatments; and 1 dog treated with an alternating protocol of doxorubicin and carboplatin was administered an additional 2 doses of cisplatin after thoracoscopic metastectomy of 2 pulmonary metastases, resulting in a total of 8 treatments. This latter dog was also treated with metronomic chemotherapy (consisting of doxycycline, piroxicam, and low-dose cyclophosphamide) and alternative therapies such as artemisinin and vascustatin.<sup>42</sup> These additional treatments and changes in chemotherapy protocols were done at the request of the owners.

Three dogs did not complete the targeted chemotherapy course with 1 dog in each group receiving 3 of 6 targeted doses of the alternating doxorubicin and carboplatin protocol, and 1 dog in the EN group receiving 1

of 4 targeted doses of carboplatin. The reasons for failure to complete the targeted chemotherapy course was owner preference for 1 dog in the CA group and, in the EN group, death because of gastric dilatation-volvulus (n = 1) or cardiomyopathy (n = 1). In the latter dog, cardiomyopathy was diagnosed preoperatively and this dog was administered a single dose of carboplatin before cessation of chemotherapy.

### Surgical Outcome—Infection

Surgical infection was diagnosed in 11 dogs resulting in an overall infection rate of 55% with a median time to infection of 74 days. The infection rate was 60% in the CA group with a median time to infection of 80 days (Table 2). Microbial culture was performed in 5 dogs in the CA group and not in 1 dog with a surgical infection. Most cultured infections were monomicrobial (n = 3) with 2 different bacteria cultured in 1 dog and no bacteria cultured in another dog. Surgical infections were graded

Table 2. Surgical infection in dogs following limb-sparing surgery with either cortical allograft or endoprosthesis

Case	Interval (days)	Culture	Severity	Treatment
<b>Cortical allograft</b>				
1	74	<i>Enterococcus faecalis</i>	Severe	Antibiotics then amputation
2	39	<i>Proteus mirabilis</i>	Severe	Antibiotics then debridement
3	—	—	—	—
4	86	No growth	Severe	Antibiotics
5	—	—	—	—
6	—	—	—	—
7	116	<i>Enterococcus faecalis</i>	Moderate	Antibiotics
8	—	—	—	—
9	19	<i>E. coli</i> and <i>Klebsiella</i> sp.	Severe	Antibiotics
10	98	No culture	Mild	Antibiotics
Median	80		Severe	
<b>Endoprosthesis</b>				
1	—	—	—	—
2	139	<i>Enterococcus faecalis</i>	Severe	Antibiotics
3	—	—	—	—
4	—	—	—	—
5	55	<i>Enterococcus faecalis</i>	Severe	Antibiotics
6	14	<i>Acinobacter</i> sp.	Moderate	Antibiotics
7	—	—	—	—
8	—	—	—	—
9	61	No growth	Mild	Antibiotics
10	238	<i>Citrobacter freundii</i>	Severe	Antibiotics then amputation
Median	61		Severe	

as mild in 1 dog, moderate in 1 dog, and severe in 4 dogs. All dogs with a positive culture ( $n=4$ ) were treated with susceptibility-directed antibiotics and empirical antibiotics were selected for dogs in which culture was either negative ( $n=1$ ) or not performed ( $n=1$ ). The dog with a negative culture was treated with cephalexin before culture being performed. Two dogs with severe infections required further surgery (debridement [ $n=1$ ] or limb amputation [ $n=1$ ]) to assist in management of the infection.

The infection rate was 50% in the EN group with a median time to infection of 61 days. Similar to the CA group, culture was performed in 5 dogs with monomicrobial infections in 4 dogs and no growth in 1 dog. Surgical infections were graded as mild in 1 dog, moderate in 1 dog, and severe in 3 dogs. All dogs with a positive culture ( $n=4$ ) were treated with susceptibility-directed antibiotics and empirical antibiotics were selected for the dog in which culture was negative ( $n=1$ ). The dog with a negative culture was treated with clindamycin before the culture being performed. One dog with a severe infection required limb amputation to resolve the surgical infection. There was no significant difference in either the surgical infection rate, infection severity, or median time to infection between the CA and EN groups (Table 1).

There was no significant association between infection and other variables such as surgical time ( $P=.219$ , power = 0.241), preservation of the ulna ( $P=.303$ , power =

0.252), percentage of radius replaced by the implant ( $P=.258$ , power = .201), and construct failure ( $P=1.000$ , power = 0.013).

#### *Surgical Outcome—Construct Failure*

Construct failure occurred in 8 dogs yielding an overall construct failure rate of 40% with a median time to failure of 237 days. Construct failure was diagnosed in 4 dogs in the CA group with a median time to failure of 309 days (Table 3). Construct failure was characterized by either screw loosening or screw breakage in either the metacarpal bone ( $n=3$ ) or radiocarpal bone and CA ( $n=1$ ). Construct failure was graded as either mild ( $n=2$ ) or moderate ( $n=2$ ). Surgical revision was required in 2 dogs in which the loosened bone screws were removed and replaced with larger diameter bone screws. In 1 dog, screw loosening was considered secondary to severe surgical infection. Limb amputation was performed in this dog to control surgical infection. The dog was not clinically affected by the screw loosening and construct failure was graded as mild because limb amputation was not performed for management of the construct failure and surgical revision would not have been necessary to manage the mild screw loosening.

Construct failure was also detected in 4 dogs in the EN group with a median time to failure of 180 days. In

Table 3. Construct failure in dogs following limb-sparing surgery with either cortical allograft or endoprosthesis

Case	Interval (days)	Construct Failure	Severity	Treatment
<b>Cortical allograft</b>				
1	207	Screw loosening: 4 distal screws	Mild	None
2	501	Screw loosening: 2 distal screws	Moderate	Screw replacement
3	253	Screw loosening: 2 allograft screws Screw fracture: radiocarpal bone screw	Moderate	Screw replacement
4	—	—	—	—
5	—	—	—	—
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	—	—	—	—
10	365	Screw loosening and fracture: 1 distal screw	Mild	None
Median	309		Moderate	
<b>Endoprosthesis</b>				
1	125	Screw loosening: 1 proximal screw Metacarpal fracture	Mild	External coaptation
2	—	—	—	—
3	—	—	—	—
4	139	Screw fracture: 5 proximal screws	Severe	Screw replacement
5	—	—	—	—
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	220	Screw loosening: 5 proximal screws Screw fracture: 1 proximal screw	Moderate	Screw replacement
10	474	Screw loosening: 1 proximal screw	Mild	None
Median	180		Moderate	



**Fig 4.** Construct failure following limb-sparing surgery with an endoprosthesis. Construct failure in dogs with limb-salvage using an endoprosthesis involved either screw loosening or breaking in the proximal aspect of the radius. This was the most severe construct failure encountered in our series and was treated with revision surgery by replacement of the proximal cortical bone screws.

contrast to the CA group where all construct failures occurred either within or distal to the CA, all construct failures in the EN group involved screw loosening or screw breakage in the proximal aspect of the radius ( $n=4$ ; Fig 4) with 1 dog also diagnosed with a metacarpal fracture at the level of the distal screw hole. In 2 dogs, construct failure was considered secondary to severe surgical infection. Construct failure was graded as mild ( $n=2$ ), moderate ( $n=1$ ), or severe ( $n=1$ ). Surgical revision was required in 2 dogs in which the loosened bone screws were removed and replaced with larger diameter bone screws. There was no significant difference in construct failure rate, severity, or median time to failure between the CA and EN groups (Table 1).

There was no significant association between construct failure and surgery time ( $P=.781$ , power=0.058), en bloc resection of the ulna ( $P=.775$ , power=0.013), bending of the plate at the implant-radiocarpal bone junction ( $P=.624$ , power=0.026), number of screws used to secure the bone plate proximal ( $P=.343$ , power=

0.152) and distal ( $P=.330$ , power=0.096) to the implant, percentage of radius replaced by the implant ( $P=.459$ , power=0.100), percentage of metacarpal coverage by the bone plate ( $P=.560$ , power=0.083), and surgical infection ( $P=1.000$ , power=0.013).

#### *Surgical Outcome—Limb Function*

Limb function was subjectively graded at various time intervals ranging from 13 to 735 days postoperatively. Limb function was assessed at study end (immediately before euthanasia) or at the time of limb amputation for the management of complications such as avascular necrosis of the digits ( $n=1$ ) or surgical infection ( $n=2$ ). Overall, limb function was graded as good to excellent in 75% of dogs with moderate lameness in 4 dogs and severe lameness in 1 dog.

In the CA group, 70% of dogs had good to excellent limb function with mild lameness in 4 dogs and no evidence of lameness in 3 dogs. The dog with avascular necrosis of the digits had a non-weight-bearing lameness immediately before limb amputation and this dog was considered to have a severe lameness and poor limb function. Two dogs with moderate lameness also had poor limb function and both dogs had surgical infections. Four other dogs in the CA group with surgical infection had either good ( $n=3$ ) or excellent limb function ( $n=1$ ).

In the EN group, limb function was graded as good to excellent in 80% of dogs with mild lameness in 6 dogs and no evidence of lameness in 2 dogs. Moderate lameness was recorded in 2 dogs, 1 with surgical infection and 1 with local tumor recurrence. Similar to the CA group, 4 other dogs with surgical infection in the EN group had either good ( $n=3$ ) or excellent limb function ( $n=1$ ). There was no significant difference in postoperative limb function between the CA and EN groups (Table 1). Furthermore, limb function was not associated with postoperative infection ( $P=.612$ , power=0.080), construct failure ( $P=.192$ , power=0.261), or local tumor recurrence ( $P=.471$ , power=0.117).

#### *Oncologic Outcome—Local Tumor Recurrence*

The disease-free and overall limb-salvage rate was 70% and 85%, respectively. Limb amputation was performed for treatment of complications in 3 dogs, including avascular necrosis of the digits ( $n=1$ , CA group) and postoperative infection ( $n=2$ , 1 dog each from CA and EN groups). Local tumor recurrence was diagnosed in 3 dogs, 1 dog in the CA group and 2 dogs in the EN group, between 101 and 342 days postoperatively (Table 4). The ulna was not resected en bloc with the radius in all 3 of these dogs, however a significant association between preservation of the ulna and local tumor recurrence was not identified

Table 4. Oncologic outcome in dogs treated with limb-sparing surgery and postoperative chemotherapy

Case	DFI (days)	MFI (days)	Metastasis Sites	Death	Survival Time (days)
<b>Cortical allograft</b>					
1	—	654	Bone	Metastasis	685
2	—	556	Lungs	Metastasis	562
3	—	—	—	Histiocytic sarcoma	499
4	—	282	Lungs	Metastasis	322
5	—	389	Lungs, liver	Metastasis	393
6	—	139	Lungs, liver, kidney	Metastasis	141
7	—	172	Lungs	Metastasis	212
8	—	133	Lungs	Metastasis	228
9	—	—	—	Hemangiosarcoma	394
10	342	427	Bone, lungs	Metastasis	430
Median	342	336			412
<b>Endoprosthesis</b>					
1	—	—	—	Cardiomyopathy	176
2	—	188	Lungs	Unknown	517
3	209	273	Lungs, spleen	Metastasis	273
4	—	154	Bone	Metastasis	289
5	—	—	—	GDV	72
6	—	—	—	Lung carcinoma	196
7	—	161	Lungs	Lost-to-follow-up	161
8	101	—	—	Cardiomyopathy	158
9	—	661	Bone, lungs	Metastasis	735
10	—	668	Bone	Metastasis	705
Median	155	188			705

DFI, local disease-free interval; MFI, metastasis-free interval

( $P = .540$ , power = 0.009). Owners declined limb amputation or further limb-sparing surgery for management of local tumor recurrence. One dog died 57 days after diagnosis of local recurrence because of cardiomyopathy, while the remaining 2 dogs were euthanized 64 and 88 days after diagnosis of local recurrence because of metastatic disease. There was no significant difference in local recurrence rate between the CA and EN groups. Local tumor recurrence did not significantly decrease survival time with a MST of 351 days in dogs with local recurrence and 562 days in dogs without local tumor recurrence ( $P = .381$ , power = 0.140).

#### Oncologic Outcome—Metastasis

Overall metastatic rate was 70% with a median MFI of 278 days. The lungs ( $n = 10$ , 71.4%) and bone ( $n = 5$ , 35.7%) were the most common sites of metastasis, with liver, kidney, and spleen also reported (Table 4). In the CA group, the metastatic rate was 80% with a median MFI of 336 days (range, 133–654 days). The metastatic rate was 60% in the EN group with a median MFI of 188 days (range, 154–668 days). There was no significant difference in either the metastatic rate or median MFI be-

tween dogs in the CA and EN groups (Table 1). Overall, the median MFI was significantly longer in dogs with surgical infection (556 days,  $P = .043$ ) compared to dogs without surgical infection (273 days).

#### Oncologic Outcome—Survival

Overall MST was 430 days. The MST was not significantly different between dogs in the CA and EN groups, with a MST of 412 days (range, 141–685 days) for dogs in the CA group and 705 days (range, 72–735 days) for dogs in the EN group (Fig 5; Tables 1 and 4). Tumor-related deaths were recorded in 12 dogs (60%), all because of metastatic disease. One dog was lost-to-follow-up after being diagnosed with pulmonary metastasis and this dog was censored from survival analysis at the time it was lost-to-follow-up (161 days). Tumors other than OSA were the cause of death in 3 dogs (splenic hemangiosarcoma, disseminated histiocytic sarcoma, and primary lung carcinoma). Three dogs died because of non-neoplastic diseases (cardiomyopathy [ $n = 2$ ] and gastric dilatation-volvulus [ $n = 1$ ]). For the 2 dogs where death was caused by cardiomyopathy, 1 dog was diagnosed with dilated cardiomyopathy before surgery and received 1 dose of carboplatin before discontinuing chemotherapy and the other dog completed a full course of chemotherapy with single-agent doxorubicin. In the latter dog, doxorubicin-induced cardiomyopathy cannot be excluded, but preoperative echocardiographic examination was within normal limits and the cumulative doxorubicin dose of 150 mg/m<sup>2</sup> was less than the cumulative cardiotoxic dose of 180–240 mg/m<sup>2</sup>. One dog died of unknown causes and has been described in detail elsewhere.<sup>42</sup> Briefly, the dog was diagnosed with hypertrophic osteopathy secondary to pulmonary metastasis and thoracoscopic metastectomy was performed to manage both conditions 211 days after

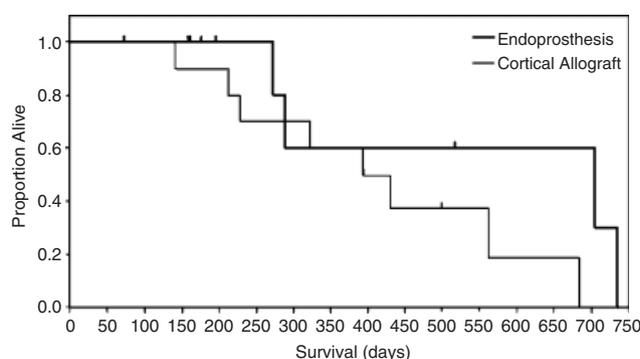


Fig 5. Kaplan-Meier survival curve for dogs treated with limb-sparing surgery using either a cortical allograft or endoprosthesis and postoperative chemotherapy. There was no significant difference in the median survival times for dogs in the cortical allograft (412 days) and endoprosthesis (705 days) groups ( $P = .146$ ). Note that each bar on the curve represents a censored event.

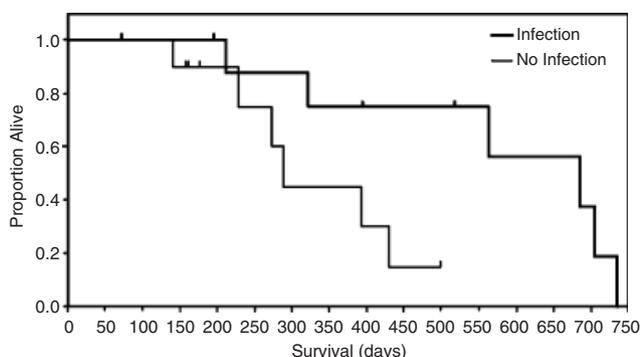
limb-sparing surgery. A further pulmonary metastatic lesion resolved after treatment with metronomic chemotherapy (consisting of doxycycline, piroxicam, and low-dose cyclophosphamide) and alternative therapies such as artemisinin and vascustatin. Subcutaneous metastases were diagnosed 203 days post-metastatectomy, but the dog did not have evidence of other metastatic disease at the time of death (517 days after limb-sparing surgery).

Overall, the MST was significantly longer in dogs with surgical infection (685 days,  $P = .034$ ) compared to dogs without surgical infection (289 days; Fig 6). The hazard ratio (HR) for infection was 24.58 (95% confidence interval, 1.45–417.66). Construct failure also significantly increased survival time with a MST of 322 days for dogs without construct failure and 685 days for dogs with construct failure ( $P = .037$ ; HR 16.82; 95% confidence interval, 1.55–182.16; Fig 7). Age did not influence survival on univariate analysis ( $P = .169$ ), but the MST for older dogs was significantly decreased on multivariate analysis ( $P = .042$ ; HR 2.06; 95% confidence interval, 1.03–4.14). Body weight ( $P = .636$ , power = 0.095), percentage of radius replaced by the implant ( $P = .580$ , power = 0.099), and local tumor recurrence ( $P = .381$ , power = 0.140) did not have a significant impact on survival time.

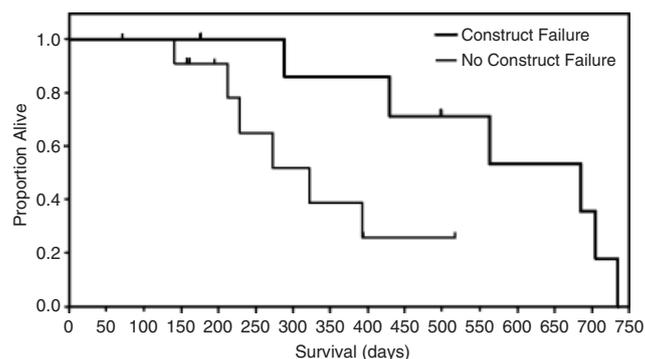
## DISCUSSION

In this prospective randomized cohort study, we compared the clinical and oncologic outcome of limb-sparing surgery using either a CA or EN in 20 dogs with spontaneously occurring, non-metastatic OSA. Our primary aim was to compare ENs with massive CAs to determine the suitability of the EN for limb-sparing surgery of the distal aspect of the radius in dogs.

Massive CAs have traditionally been used for limb-sparing surgery in both dogs<sup>3–6,9</sup> and humans.<sup>16–21</sup> The



**Fig 6.** Kaplan–Meier survival curve for dogs treated with limb-sparing surgery and postoperative chemotherapy with and without postoperative infection. The median survival time of 685 days for dogs with infection was significantly better than the median survival time of 289 days for dogs without infection ( $P = .034$ ). Note that each bar on the curve represents a censored event.



**Fig 7.** Kaplan–Meier survival curve for dogs treated with limb-sparing surgery and postoperative chemotherapy with and without construct failure. The median survival time for dogs with construct failure was 685 days, which was significantly better than the 322 day median survival time for dogs without construct failure ( $P = .037$ ). Note that each bar on the curve represents a censored event.

use of CAs requires bone banking facilities and time commitments for bone harvesting and the cataloging and matching of donors and recipients. Furthermore, the use of CAs is associated with a high complication rate with infection reported in up to 70%, construct failure in 11%–60%, and local tumor recurrence in up to 28% of dogs.<sup>3–6</sup>

Alternative limb-sparing techniques have been investigated in an attempt to decrease the incidence of postoperative complications, particularly infection. These techniques include vascularized, pasteurized, and irradiated autografts and intercalary bone transport with circular external fixators.<sup>7,8,23,24,10,11</sup> Clinical use of ENs has not been reported in dogs, but ENs are commonly used in humans for limb-sparing surgery, especially for joint preservation<sup>17–22,25,26</sup> and expandable ENs in children so that the growth rate of the salvaged limb can be matched to the contralateral limb.<sup>26,27,43–51</sup>

The EN we used was recently compared with cortical bone grafts in a cadaveric biomechanical study of axial loading until failure.<sup>22</sup> Both implants were considered suitable for limb-sparing surgery of the distal aspect of the radius as the yield point for both the cortical bone graft and EN exceeded the forces transmitted through the thoracic limb at a walk, trot, and jump from 94 cm height.<sup>22</sup> However, EN-reconstructed limbs were significantly stronger and up to 33% stiffer than cortical bone graft-reconstructed limbs.<sup>22</sup> These results supported the use and investigation of the EN for limb-sparing surgery of the distal aspect of the radius in dogs.

### Surgical Outcome—General Considerations

There were no clinically significant differences in surgical outcome between dogs in the CA and EN groups. A type II error is possible because the statistical power of these anal-

yses was low. Depending on the examined variable, between 220 and 620 dogs would be required to achieve a power of 85%. Subjectively, limb-sparing surgery with the EN was less complicated as intricacies involved with CAs were avoided, such as thawing the CA, osteotomizing the CA to the appropriate length, and filling the intramedullary canal of the CA with PMMA. However, despite surgical time being 15 minutes quicker in the EN group, there was no significant difference in surgical time between the CA and EN groups. The percentage of radius replaced by the EN was significantly greater than CAs because the EN is only available in a 122 mm length. Although such large resections increase the chance of excising the tumor with complete histologic margins, a greater range of EN lengths would enable the surgical oncologist to more appropriately match the EN length to both the tumor and dog size.

#### *Surgical Outcome—Infection*

Overall postoperative infection rate was 55% and there were no significant differences in infection rate, severity, or median time to infection between the CA and EN groups. Infection was defined as the presence of  $\geq 1$  draining sinus tracts at the surgery site. However, of 11 dogs with infection, 1 dog did not have microbial culture performed and 2 dogs had negative cultures. Defining these draining sinus tracts as infections may not be accurate as they may have been caused by immunogenic reactions to the CA or secondary to OPLA-Pt induced necrosis. Despite this possibility, we believe the definition is correct because 1 of the negative cultures occurred in the EN group where an immunologic reaction to surgical steel is very unlikely and similar infection rates (31–39%) have been reported in canine limb-sparing surgery where OPLA-Pt was not used.<sup>3,4</sup> Negative cultures with true infections can be caused by errors in either tissue sampling, preparation, transport, or culturing, or administration of antibiotics before microbial culturing. Both dogs with draining sinus tracts and negative cultures in our study had antibiotics administered before culture.

In humans, postoperative infection rate is significantly higher for allograft-arthrodesis limb-salvage and an immunologic response to soluble proteins in the CA has been implicated as the primary causative factor in these infections.<sup>16,25</sup> The use of a rigorous histocompatibility matching process and immunosuppressive drugs have been proposed as methods of reducing the infection rate in limb-sparing surgery involving massive CAs.<sup>16</sup> The limitations to these approaches, particularly combining immunosuppressive drugs with chemotherapy agents, precludes their routine use for dogs undergoing limb-sparing surgery.

We had hoped that the infection rate and severity would be substantially reduced with the use of the EN because the immunologic response associated with CAs

would be avoided. Furthermore, the infection rate in humans with non-expandable endoprosthetic reconstructions is frequently less than reported for CAs (1.2–13.8% compared with 11.7–30%), but a controlled study or meta-analysis has not been performed to objectively analyze the influence of implant type on the incidence of infection.<sup>16–21,26,27,43–52</sup> The use of a large volume of implants and foreign material has been proposed as a cause of postoperative infection after limb-sparing surgery.<sup>53</sup> Total hip arthroplasty (THA) is the only other procedure routinely performed in dogs involving a large volume of implants, but the postoperative infection rate after THA in recent reports is  $<2.3\%$ .<sup>54–58</sup> Hence, infection is most likely caused by factors specific to limb-sparing surgery and regardless of the type of implant used.

Soft tissue coverage is an important determinant of postoperative infection for limb-sparing surgery in humans as the infection rate is significantly higher in regions with poor soft tissue coverage (e.g., proximal tibia)<sup>46,59</sup> and the infection rate is significantly reduced by improving soft tissue coverage and local blood supply with muscle flaps.<sup>44,60,61</sup> Furthermore, the infection rate for limb-sparing surgery of the proximal humerus in dogs, which has much greater soft tissue coverage than the distal antebrahium, is only 35%<sup>9</sup> compared with a rate of up to 70% in the distal aspect of the radius.<sup>3–6</sup> The role of free microvascular muscle flaps in the prevention and treatment of limb-sparing-associated infections warrants investigation. Chemotherapy also significantly increases the risk of postoperative infections after limb-salvage in humans,<sup>16,59,62</sup> but the clinical importance of this finding is limited because of the necessity of chemotherapy in the curative-intent treatment of dogs with OSA.<sup>1,2</sup>

#### *Surgical Outcome—Construct Failure*

Construct failure was relatively common complication and occurred in 40% of our dogs. In contrast to many studies, construct failure was frequently not associated with clinical signs and did not have a dramatic impact on limb function and quality of life. There were no significant differences in the rate, severity, or median time to construct failure between dogs in the CA and EN groups. Furthermore, construct failure was not associated with any intraoperative or postoperative factors. The lack of association of construct failure with infection was surprising considering infection significantly increases the risk of limb-salvage failure in both dogs and humans because of decreased cortical thickness and integrity.<sup>10,16,17,19,27,63</sup> A post-hoc power analysis showed that the chance that we could identify a statistically significant difference with our sample size was only 1.3%, and hence the failure to identify an association between construct failure and infection may be because of a type II error.

In a biomechanical study of axial loading to failure, thoracic limbs reconstructed with an EN performed significantly better than those reconstructed with a cortical bone graft.<sup>22</sup> However, axial loading is an acute test and does not evaluate the effects of cyclic loading and stresses on construct stability. The EN and cortical bone graft-reconstructed thoracic limbs were also tested to 100,000 cycles without evidence of failure, but clinically 100,000 cycles is analogous to only 22 days of activity.<sup>22</sup> We found the median time to construct failure was 237 days and the earliest failure was reported at 125 days. This finding emphasizes the difficulty in extrapolating biomechanical results to clinical situations and the importance of cyclic loading on the long-term performance of limb-sparing constructs.

In the aforementioned biomechanical study, axial loads sustained before failure were significantly greater with shorter implant lengths, regardless of whether the implant was an EN or CA.<sup>22</sup> The percentage of radius replaced by the implant was the only significant difference between CA and EN groups in our dogs. The median percentage of radius replaced by CAs and ENs was 48.6% and 60.9%, respectively. With less bone available for fixation of the bone plate in the proximal aspect of the radius EN group, it is possible that the reduced number of bicortical screws increased susceptibility to cyclic loading and subsequent screw loosening or breakage. However, it should also be noted that there were no significant differences in the number of bicortical screws in the proximal aspect of the radius between the CA and EN groups and the median number of cortices engaged in both groups (15 cortices in the CA group and 11 cortices in the EN group) was greater than current AO/ASIF recommendations for bone plate fixation of standard fractures.<sup>31</sup> A 98 mm EN is currently being produced because of concerns that the 122 mm EN length may contribute to construct failure either directly by replacing an excessive percentage of radius or indirectly by limiting bone stock for bicortical screw purchase in the proximal aspect of the radius.

Cortical allografts are incorporated by a healing process called creeping substitution.<sup>64</sup> Because of the size of the massive CAs used in limb-sparing surgery, this process can take >2 years for completion.<sup>1,64</sup> The MST for dogs with appendicular OSA treated with curative-intent surgery and chemotherapy is 235 to 366 days.<sup>1,2,32-41</sup> Hence, CAs essentially act as a spacer in the reconstructed limb because most dogs will die of their disease before allograft incorporation. Gebahardt et al<sup>17</sup> cited that a major advantage of CAs in limb-sparing surgery is that construct failure is less likely to occur after allograft incorporation. Recent studies have shown that this is not necessarily correct as CA strength decreases with time because of an increase in prevalence of microfractures and a decrease in bone mineral density.<sup>63</sup> Thus, in dogs, the stability of limb-salvage constructs using CAs is po-

tentially affected by lack of allograft incorporation and decreased strength during the postoperative lifespan of the majority of dogs with appendicular OSA.

The EN also acts as a spacer and this stimulated our interest in investigating the EN as an alternative to CAs. Although not significant, the median time to construct failure was 180 days in the EN group and 309 days in the CA group. The material properties of CAs and surgical steel ENs are different and this may have influenced the time to construct failure and modes of failure. The modulus of elasticity for cortical bone and surgical steel is 16–28 and 200 GPa, respectively.<sup>65</sup> As CAs will have a similar modulus of elasticity to host cortical bone, weight-bearing forces will be transmitted evenly through the construct with minimal risk of stress concentration. Construct failures in the CA group were associated with screw loosening in either the metacarpus, radiocarpal bone, or CA. In contrast, all construct failures in the EN group involved screw loosening or breaking in the proximal aspect of the radius. The difference in the modulus of elasticity between the surgical steel EN and host cortical bone may result in poor load sharing and concentration of weight-bearing forces at the proximal EN-host bone interface resulting in higher cyclic loading at this point and an increased risk of failure proximal to the EN. Mechanical and biologic approaches may decrease the risk of construct failure. A locking bone plate, in which bone screws lock into both the bone plate and bone, significantly improves screw pullout resistance<sup>66</sup> and may reduce the incidence of screw loosening after limb-sparing surgery with either a CA or EN. Biologically, methods that promote osseous integration between the EN and host bone, such as hydroxyapatite coating and extracortical bone bridging fixation,<sup>46,67,68</sup> may improve load transfer and decrease stress concentration at the proximal interface and thereby address a possible causative factor for construct failure in the EN group.

#### *Surgical Outcome—Limb Function*

Limb function was subjectively graded as good to excellent in 75% of dogs which is similar to the 69 to 72% cited in earlier reports of allograft-arthrodesis limb-salvage of the distal aspect of the radius in dogs.<sup>3,4</sup> There was no significant difference in limb function between dogs in the CA and EN groups.

A limitation of our study was the subjective criteria used to assess lameness and limb function. Objective assessment with force plate analysis would have been preferable, particularly with the prospective design of this study, but was not possible because most dogs could not return at regular intervals because of distance and time constraints. The severity of lameness after limb-sparing surgery may have been overestimated as most assess-

ments were done at time points in which limb function would be expected to be poor, such as immediately before limb amputation for the management of complications in 3 dogs and before euthanasia in a further 3 dogs with local tumor recurrence. However, an association between limb function and infection, construct failure, and local tumor recurrence was not identified.

Local disease-free and overall limb-salvage rates were 70% and 85%, respectively. The surgical revision rate was 20% and limb amputations were performed in 3 dogs, including 2 dogs for surgical infection but none for local tumor recurrence. Similar to human reports, surgical revision is usually required for management of construct failure and limb amputation for deep infections.<sup>43–45,59</sup>

#### *Oncologic Outcome—Local Tumor Recurrence*

There were no significant differences in oncologic outcome between dogs in the CA and EN groups. The overall rate of local tumor recurrence was 15%, which is within the 11–28% range reported in other studies of limb-salvage for dogs with distal radial tumors.<sup>3,6,8,24</sup> In humans, local recurrence after limb-sparing surgery is significantly more likely if tumor resection is incomplete.<sup>34,69,70</sup> However, all tumors were resected with complete histologic margins in our study. Most local tumor recurrences occur in the region adjacent to the resected bone tumor, particularly the distal antebrachium.<sup>4,70</sup> In our dogs, local tumor recurrence occurred in the distal ulna and only in dogs where the ulna was preserved. En bloc resection of the ulna with distal radial tumors, regardless of whether there is macroscopic evidence of tumor extension into the ulna, may decrease the risk of local tumor recurrence and warrants further investigation. En bloc resection of the ulna with the distal aspect of the radius does not negatively affect stiffness or strength of thoracic limbs reconstructed with either cortical bone grafts or ENs when tested in axial loading.<sup>22</sup> The effects of en bloc resection of the ulna on long-term stability of the limb-sparing constructs is unknown, but resection of the ulna was not associated with construct failure in this and other studies.<sup>5</sup>

Local tumor recurrence has been reported to have either a negative<sup>9,16,17,34,69–72</sup> or negligible<sup>73</sup> impact on survival time in dogs and humans with OSA. In our study, local tumor recurrence did not adversely affect survival time, although all 3 dogs died within 88 days of local recurrence because of either distant metastasis or reasons unrelated to the primary tumor. Based on a post-hoc power analysis, the ability to detect a statistically significant result was only 14% and 100 dogs would be required to achieve a power of 78%. As a result, the lack of effect of local tumor recurrence on survival time may be because of a type II error (i.e., low statistical power because of

small sample population). A close association between local tumor recurrence and the development of distant metastasis has been reported in other studies.<sup>3,10,17,70</sup> Limb amputation or a second limb-sparing surgery can be performed to resect the recurrent tumor,<sup>1,2,70,73</sup> but this should only be considered after complete staging has been performed to exclude metastatic disease.

#### *Oncologic Outcome—Metastasis and Survival*

The overall median MFI and MST were 278 and 430 days, respectively. As expected, there were no significant differences in median MFI and MST between dogs in the CA and EN groups. Resection of the local tumor with either limb amputation or limb-sparing surgery does not influence overall survival time in dogs with OSA.<sup>1</sup> Chemotherapy is the only treatment proven to significantly prolong survival time as the MST for dogs with appendicular OSA treated with amputation alone is 119–168 days compared with 235–366 days for dogs treated with limb amputation and adjuvant chemotherapy.<sup>32–41</sup> Cisplatin, carboplatin, and doxorubicin are the most active agents for treatment of canine appendicular OSA.<sup>32–41</sup> These agents are used either alone or in combination,<sup>32–41</sup> but no significant differences in oncologic outcome have been identified between these different chemotherapy drugs and protocols (personal communication: J.M. Liptak, Veterinary Cancer Society, 2001; and N.J. Bacon, Veterinary Cancer Society Mid-Year Symposium on Canine Osteosarcoma, 2006). Hence, it is unlikely that the different postoperative chemotherapy protocols used in this study had any impact on survival times. In our study, regardless of implant type, age, construct failure, and infection were prognostic factors for survival.

**Age.** The influence of age on prognosis is contradictory as both young and old age are cited as poor prognostic factors in dogs with appendicular OSA.<sup>74,75</sup> Older age was prognostic in our study. Increasing age may negatively impact survival because of a decreased tolerance to chemotherapeutic agents or resistance to the development of metastatic disease.<sup>74</sup>

**Construct failure.** Construct failure has not been previously identified as having a positive impact on survival in either dogs or humans after limb-sparing surgery for appendicular OSA. In our study, dogs without construct failure were 17 times more likely to die as a result of their tumor than dogs with construct failure. Infection increases the risk of construct failure<sup>10,16,17,19,27,51,63</sup> and, in this and other studies, also improves survival time.<sup>6,76</sup> However, infection was not associated with construct failure in our study and hence an interaction between infection and construct failure cannot be attributed to the improved survival time seen in dogs with construct failure. A reverse effect (i.e., dogs that live a longer time are more likely to have

construct failure) is also unlikely as the median time to construct failure was 237 days whereas the MST for dogs with construct failure was substantially longer at 685 days. Construct failure was not catastrophic and usually consisted of either screw loosening or breaking. Constant screw motion may have incited an inflammatory and subsequent immunologic reaction similar to the mechanisms by which infection have been proposed to improve survival time.

**Infection.** Postoperative infection significantly improved both the median MFI and MST in dogs treated with either CA or EN limb-salvage and adjuvant chemotherapy. The median MFI for dogs with non-infected and infected limb-salvage constructs was 273 and 556 days, respectively. Similarly, the MST for dogs with non-infected and infected limb-salvage constructs was 289 and 685 days, respectively. The positive impact of infection on survival time has been identified in other studies of limb-sparing surgery in dogs.<sup>6,76</sup> Dogs without postoperative infections were 25 times more likely to die as a result of their tumor compared with dogs with limb-salvage-associated infections in this study and 2 times more likely in another study.<sup>6</sup> A similar relationship has not been identified in musculoskeletal tumors in humans, but significantly improved survival times have been reported with postoperative infection after resection of bronchogenic and laryngeal carcinomas.<sup>77-79</sup> The mechanisms responsible for this prolonged MFI and survival have not been elucidated, but an upregulation of either cell-mediated or humoral antitumor immunity has been proposed.<sup>6</sup> For instance, enhanced natural killer cell and immune effector cell activity by a lyophilized extract of *Streptococcus pyogenes* has a beneficial effect in humans with terminal malignancies,<sup>80-82</sup> and administration of a liposome-encapsulated macrophage activator, muramyl tripeptide, in combination with cisplatin, significantly improves disease-free interval and survival times in dogs with OSA.<sup>83</sup>

## CONCLUSION

The EN provides a viable alternative to the traditional CA for limb-sparing surgery of the distal aspect of the radius in dogs. There were no significant differences in either surgical or oncologic outcome between the 2 implant types. There was no decrease in either the rate or severity of postoperative infection with the use of the EN. Unlike a biomechanical study comparing cortical bone grafts and ENs,<sup>22</sup> there were no differences in the incidence of construct failure and this is most likely due to the effects of long-term cyclic stresses. In comparison with CAs and other reported limb-sparing techniques, the advantages of the EN include the immediate availability of an off-the-shelf implant and no need for specialized equipment, bone banking facilities, or access to external beam radiation therapy.

Regardless of the implant used for limb-sparing surgery of the distal aspect of the radius, the potential role of en bloc ulna resection in decreasing the risk of local tumor recurrence warrants further investigation. Postoperative infection is the most common complication associated with limb-sparing surgery but, in our series, infection did not have a negative impact on limb function and significantly improved both median MFI and MST. Identification of the mechanisms by which infection improves oncologic outcome may provide an opportunity to improve the outcome of children and dogs with OSA.

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