Annals of Surgical Oncology, **11**(7):705–713
DOI: 10.1245/ASO.2004.10.008

Biodegradable Cisplatin Polymer in Limb-Sparing Surgery for Canine Osteosarcoma

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Background: The rate of local recurrence of osteosarcoma after limb-sparing surgery in dogs and humans has been reported up to 28%. The primary purpose of this study was to determine whether a biodegradable cisplatin-containing implant (OPLA-Pt), inserted into the limb-sparing surgery site at the time of surgery, would decrease the rate of local recurrence. Secondary aims included evaluation of systemic toxicity associated with the release of cisplatin from the implant and identification of prognostic factors associated with limb-sparing surgery for osteosarcoma in dogs.

Methods: Eighty dogs with spontaneously occurring osteosarcoma were treated with limb-sparing surgery. They were randomized to receive the biodegradable implant either without cisplatin (control group) or with cisplatin (OPLA-Pt group) and were targeted to receive four doses of an adjuvant cisplatin chemotherapy protocol.

Results: Although this was not statistically significant ($P = .071$), dogs in the OPLA-Pt group were 53.5% less likely to develop local recurrence than dogs in the control group. There were no significant differences in systemic toxicity between treatment arms. Incomplete surgical resection, absence of infection, and fewer than four doses of adjuvant chemotherapy had a significant correlation with local recurrence and survival according to univariate analyses, although only incomplete surgical resection remained significant for local recurrence after multivariate analysis.

Conclusions: Local tumor recurrence may be decreased after limb-sparing surgery by use of biodegradable implants impregnated with chemotherapeutic agents.

Key Words: Osteosarcoma—Limb-sparing surgery—Local chemotherapy—Local tumor recurrence.

The local control of appendicular osteosarcoma (OSA) has undergone a progressive shift from amputation to various types of limb salvage.[1–11] Limb-sparing surgery should not negatively affect local recurrence or survival, delay adjuvant therapy, increase the risk of complications, or result in inferior limb function in comparison with amputation.[12] However, unlike amputation, limb-sparing surgery often involves marginal resection of the primary tumor, and this can result in a local recurrence rate of up to 28%.[4,5,7,8,10,12] Neoadjuvant chemotherapy has been proposed to downstage the tumor and increase the possibility of achieving wide and complete resection.[1,4,12] However, local recurrences are still reported, and, furthermore, amputation is often required to manage recurrent disease, thus compromising the original intention of limb-sparing surgery and possibly increasing the risk of distant metastasis and death.[5,13,14]

Local tumor recurrence occurs as a result of incomplete surgical resection or residual neoplastic cells in the soft tissue of the surgical site after marginal resection.[4,12] The role of systemic chemotherapy in preventing local recurrence with residual postoperative microscopic dis-

Received October 9, 2003; accepted March 12, 2004.

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ease is unknown. Intracavitary chemotherapy results in an increased local concentration of chemotherapy when compared with systemic chemotherapy. Exposure of surface cells within a surgical wound to a high local chemotherapeutic concentration may effectively kill tumor cells after incomplete resection.[15–20] Furthermore, lethal injury to tumor cells may be enhanced by sustained exposure to a cytotoxic agent throughout the cell cycle.[21–23] Intralesional sustained-release cisplatin has been associated with significant improvements in local tumor control in a number of different types of naturally occurring canine cancers, including oral malignant melanoma,[17] cutaneous squamous cell carcinoma,[18] soft tissue sarcoma,[19] and other types of neoplasia.[14]

A biodegradable implant (open cell polylactic acid; OPLA; Kensey Nash Corp., Exton, PA) containing 8% cisplatin (OPLA-Pt) by weight has been investigated in experimental and naturally occurring tumors in animals.[16,19,20,23] The rate of local recurrence is significantly reduced for mice with marginally resected mammary carcinoma[20,23] and dogs with incompletely resected soft tissue sarcoma[19] after implantation of OPLA-Pt into the surgical wound. Furthermore, in the mammary carcinoma model in mice, metastasis-free interval and survival time were significantly improved with OPLA-Pt compared with intraperitoneal cisplatin.[20,23]

Cisplatin is commonly used in the adjunctive management of appendicular OSA in humans and dogs.[1–3,6,9,11,24–31] Cisplatin, alone or in combination with other chemotherapeutic agents, significantly improves metastasis-free interval and survival time in dogs after definitive local surgery.[1,24,26–29,31] However, adverse effects after the systemic administration of cisplatin include nephrotoxicity, thrombocytopenia, and neutropenia.[25,32–36] Intracavitary OPLA-Pt is associated with a very low risk of systemic toxicity, in addition to improved local cytotoxicity, even with doses exceeding the maximally tolerated intravenous canine dose of 70 mg/m^2.[16,23,30] Straw et al.[16] showed that the area under the curve (AUC) for the total platinum concentration plotted against time for the first 21 days after OPLA-Pt implantation was 29 times greater than the AUC for an equivalent single dose of intravenous cisplatin, suggesting that the systemic benefits and low risk of systemic toxicity associated with OPLA-Pt are the result of a low but sustained serum concentration of cisplatin.

The purpose of this prospective, randomized study was to evaluate the rate of local tumor recurrence after limb-sparing surgery with and without intracavitary OPLA-Pt for dogs with appendicular OSA. A secondary aim was to assess systemic toxicity associated with OPLA-Pt and prognostic factors for limb-sparing surgery in dogs with OSA. We hypothesized that the cisplatin released from OPLA-Pt would decrease local tumor recurrence and have minimal systemic toxicity.

METHODS

Selection Criteria

This was a randomized, prospective trial that included 80 client-owned dogs referred to a single institution for treatment of spontaneously occurring OSA from 1990 to 1995. Sample size and power estimations were based on the primary end point (time to local recurrence). With 80 dogs, the power to detect a difference of 25% in the local recurrence rate was estimated to be 87% if all dogs survived to 12 months after surgery. However, because all dogs did not survive to 12 months, the actual power decreased to 76%. Dogs with OSA of the distal radius and ulna were selected because of the high frequency of involvement of this region, the paucity of soft tissue coverage ensuring marginal resection, and good to excellent postoperative limb function after limb-sparing surgery.[1,2,4,6] The Institutional Animal Care and Use Committee approved all procedures performed in these dogs.

Procedures

Baseline data included hematology, serum biochemistry profile, urinalysis, regional radiographs, three-view thoracic radiographs, and needle-core biopsy of the bone lesion. The primary tumor and affected bone were radiographed, and the percentage length of neoplastic involvement of the affected bone was determined. Criteria for inclusion in the trial included histological confirmation of OSA, tumor involvement of $<$60% of the bone length, absence of clinical and radiographical evidence of distant metastasis, and otherwise good physical health. Tumors were staged according to the system recommended by the American Joint Committee for Cancer at the time this study was conducted, which included tumor grade, intracompartmental or extracompartmental bone involvement, and presence or absence of metastatic disease.[1]

Limb-sparing surgery was performed as previously described.[1,2,4] Briefly, a longitudinal incision was made over the radius or ulna, and the tumor was exposed by using a combination of blunt and sharp dissection. The distal and proximal extent of bone resection was established by disarticulating the distal radius or ulna from the carpus and by performing a transverse osteotomy 5 cm proximal to the proximal radiographic limit of bone involvement, respectively. The resected bone specimen was completely immersed in India ink, fixed in 10% neutral buffered formalin, decalcified, processed into

large paraffin blocks, sectioned, stained with hematoxylin and eosin, and assessed histologically for completeness of resection.

A massive cortical allograft was used to reconstruct the osseous defect. The cortical allograft was harvested by using an aseptic technique and stored at −70°C. During surgery, the intramedullary cavity of the allograft was filled with antibiotic-impregnated methylmethacrylate, and the allograft was secured to the adjacent bony column with a bone plate.[1] Reconstruction of the distal radius necessitated pancarpal arthrodesis, although this was not required for ulnar resection. The surgical wound was copiously lavaged with isotonic saline, and a closed-suction drain was inserted adjacent to the reconstructed diaphyseal bone. Open cell polylactic acid (OPLA) implants, divided into 10 to 15 segments, were placed into the wound adjacent to the allograft and previous tumor site (Fig. 1).

The biodegradable polymer was composed of two groups of D,L-polylactic acid synthesized from the same monomer but with two different molecular weights. Fifty percent of the polymer was high molecular weight (350,000), and 50% was low molecular weight (34,000). Cisplatin was added to the low-molecular-weight polymer at a dose of 40 mg cisplatin per 500 mg of polymer, resulting in an 8% yield of cisplatin by total weight of polymer. The polymer was then sterilized with 25 kGy of gamma radiation.[16] After irradiation, the molecular weights of the high and low fractions were 235,067 and 52,938, respectively. In a surgeon-blinded process, 40 dogs were randomly assigned, by using a computerized randomization algorithm, to receive OPLA with cisplatin 60 mg/m^2 (OPLA-Pt group), and 40 dogs received an equivalent amount of OPLA without cisplatin (control group).

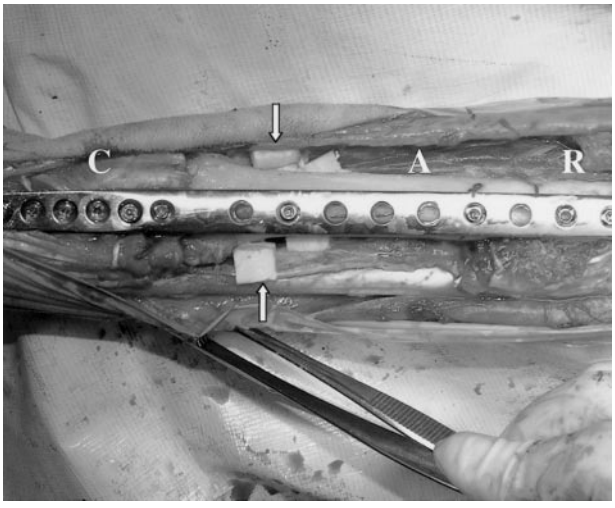

FIG. 1. Intraoperative image of an allograft-arthrodesis limb spare of the distal radius in a dog with OPLA-Pt (*arrows*). *C*, carpus; *A*, allograft; *R*, radius.

Two milliliters of wound fluid was collected from the active suction drain on postoperative day 1, immediately before removal of the drain, and 2 mL of serum was collected on days 1, 2, 3, 5, 7, and 21. The total platinum concentration in wound fluid and serum was calculated by using atomic absorption spectrophotometry and was evaluated by using a curve-stripping software package (Rstrip Exponential Stripping and Parameter Estimation; Micromath Scientific Software, Salt Lake City, UT). The AUC of the mean serum total platinum concentration versus time curve was calculated for integrals to infinity by use of the trapezoidal rule of numerical integration.[37]

Dogs were allowed to recover from surgery and were returned to the care of their owners within 3 days. Antibiotics and chemotherapy were administered to all dogs. Antibiotic prophylaxis consisted of cephazolin (administered intravenously during surgery and for 24 hours after surgery) and cephalexin or trimethoprim-sulfadiazine (administered orally until 3 weeks after finishing systemic chemotherapy).

Cisplatin was administered intravenously at 70 mg/m^2 concurrently with a previously published diuresis protocol.[1] All dogs were targeted to receive four doses of cisplatin starting 3 weeks after surgery and at 3-weekly intervals. Carboplatin (300 mg/m^2) was administered instead of cisplatin if nephrotoxicity developed, and chemotherapy was stopped if bone marrow suppression or renal toxicity was sustained after any given dose of either cisplatin or carboplatin.

Dogs were assessed at regular intervals. Physical examination and regional and three-view thoracic radiographs were performed monthly for 3 months and then every 3 months thereafter. Local recurrence or metastasis was confirmed by biopsy. In some dogs, recurrent or metastatic disease was further treated with a variety of techniques such as repeat limb spare and OPLA-Pt (n = 7), amputation (n = 5), pulmonary metastasectomy (n = 5), and palliative radiotherapy (total dose of 20 Gy divided into three to five fractions; n = 16).

The development of an infection at the surgery site was confirmed by microbial culture. Dogs were treated with appropriate antibiotics on the basis of antimicrobial sensitivity results. If the infection was resistant to antibiotic therapy, then wound debridement, removal of residual polymer material, and implantation of antibiotic-impregnated methylmethacrylate beads was performed.[38]

Dogs were euthanized at the request of the owners when recurrent or metastatic disease became unmanageable or with the development of a serious unassociated

condition. A complete necropsy was performed on 77 dogs, and the presence and site of local recurrence and metastasis were recorded. The spared bone and soft tissue were sectioned in a sagittal plane and evaluated for local recurrence by both gross and histological examination. The remaining long bones and axial skeleton were sectioned longitudinally and assessed grossly and histologically for osseous metastasis.

Statistical Analyses

The statistical analyses were specified before the accrual of cases. Preliminary descriptive analyses were used to determine whether randomization equally allocated dogs into each treatment group on the basis of demographic and prognostic characteristics. These characteristics included age, sex, body weight, radiographical appearance, bone involved, level of bone involvement, tumor histological subclassification, percentage of tumor necrosis, surgical margins, and survival outcome (local recurrence, metastasis, and cause of death). Analyses were performed with Fisher's exact test to test the equality of percentages of dogs in each category for categorical data and with one-way analysis of variance for equality of means for continuous variables.

Univariate and multivariate analyses were used to evaluate the influence of prognostic variables on local recurrence and survival. Prognostic variables included the bone affected, surgical margins, cisplatin levels from the active suction drain, peak serum cisplatin concentration, AUC, postoperative infection, number of chemotherapy treatments, and blood urea nitrogen (BUN) and creatinine levels. Univariate analyses were performed with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model for local recurrence, treatment failure, and survival. Kaplan-Meier life-table analysis was also used to analyze the statistical effects of prognostic variables on survival.

Fisher's exact test was used to assess differences in the incidence and severity of bone marrow toxicity, gastrointestinal toxicity, renal toxicity, and peripheral neuropathy between the control and chemotherapy groups. Other treatment-related adverse effects and clinical indicators of health status were also compared by using Fisher's exact test. Results were considered statistically significant with P values $<.05$.

RESULTS

Local Recurrence

The presentation of dogs included in this study was consistent with spontaneously occurring canine OSA; most were large, purebred, middle-aged dogs, and there was no sex predilection.[1] Diagnostic and staging procedures confirmed a high-grade OSA in all dogs, with extensive soft tissue involvement (stage IIB) confined to either the distal radius or ulna and with no evidence of distant metastatic disease.

Limb-sparing surgery was performed in all dogs, and all survived and were available for further evaluation. There were no statistical differences between the control and OPLA-Pt groups in terms of age ($P = .970$), sex ($P = .555$), body weight ($P = .378$), radiographical appearance ($P = .727$), tumor location in either the radius or ulna ($P = .263$) or within the bone ($P = 1.000$), tumor histology ($P = 1.000$), percentage tumor necrosis ($P = .401$), surgical margins ($P = .502$), metastasis ($P = .808$), or cause of death ($P = .178$).

Local recurrence was diagnosed in 37 dogs (46.3%): 13 in the OPLA-Pt group (32.5%) and 24 in the control group (60%). Local tumor recurrence was diagnosed clinically in 22 dogs and microscopically at necropsy in 15 dogs. The difference in the rate of local tumor recurrence between the control and OPLA-Pt groups was not significant, but a trend was noted ($P = .071$). Furthermore, dogs in the OPLA-Pt group were 53.5% less likely to experience local recurrence than dogs in the control group (hazard ratio range, .272–1.055; Fig. 2). The mean and median times to local recurrence were 325 and 302 days in the control group, respectively. The mean time to local recurrence in the OPLA-Pt group was 347 days; however, the median time to local recurrence could not be calculated because 27 of the 40 dogs were censored from analysis because of unrelated or tumor-related death before local recurrence. There was no significant

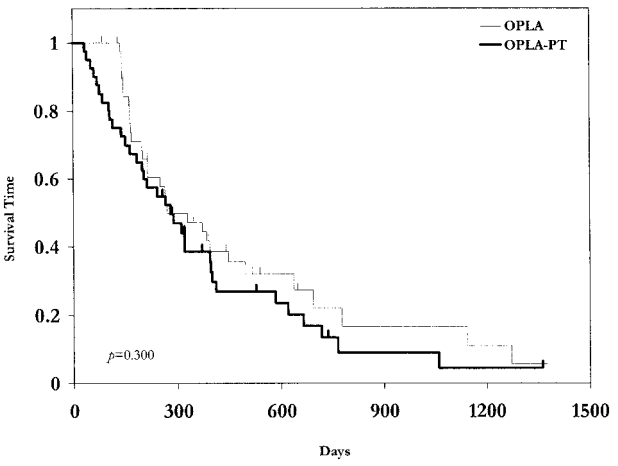

FIG. 2. Kaplan-Meier survival curve for dogs without local recurrence at the time of death. OPLA, open cell polylactic acid without cisplatin (control group); OPLA-PT, open cell polylactic acid with cisplatin.

difference between treatment groups when comparing the time to local recurrence in the 25% quartile: 132 days in the control group and 188 days in the OPLA-Pt group ($P = .100$). Univariate analysis revealed that local recurrence was significantly less likely to occur after infection ($P = .031$) and more likely with OSA in the radius ($P = .014$), incomplete resection ($P = .015$), and fewer than four chemotherapy treatments ($P = .024$). However, only incomplete resection was predictive of local recurrence according to multivariate analysis ($P = .018$).

Marginal or intralesional resection of the tumor was performed in all dogs. Resection of the bone tumor was considered marginal in most dogs when dissection continued along but did not disrupt the tumor pseudocapsule. Intralesional resection was recorded with disruption of the tumor capsule, intramedullary extension of the tumor, and evidence of a pathologic fracture of the articular surface of the distal radius. There was no evidence of gross disease after limb-sparing surgery in any dog. Resection was histologically confirmed as incomplete with positive margins in 37 dogs: 20 dogs from the OPLA-Pt group and 17 dogs from the control group. Univariate analysis revealed that incomplete resection was predictive of local recurrence ($P = .015$) and survival ($P = .018$). The 6-month survival rate for dogs with complete and incomplete surgical margins was 68.2% and 43.8%, respectively, in the control group and 84.2% and 45.0% in the OPLA-Pt group. The 12-month survival rate for dogs with complete and incomplete surgical margins was 52.4% and 26.7%, respectively, in the control group and 50.0% and 21.1% in the OPLA-Pt group. According to multivariate analysis, only incomplete resection was predictive of local recurrence ($P = .018$).

The median time to local recurrence was 832 days after complete resection and 256 days after incomplete resection. This difference was statistically significant ($P = .004$), and local recurrence was 2.62 times more likely after incomplete resection (hazard ratio range, 1.347–5.074). Furthermore, OPLA-Pt had a significant effect on the time to local recurrence after incomplete resection ($P = .004$). The time to local recurrence in the 25% quartile after complete resection was not significant: 142 days in the control group and 320 days in the OPLA-Pt group ($P = .190$). There was a significant difference between treatment groups when they were stratified into complete and incomplete surgical resection because, after incomplete resection, the median time to local recurrence in the control and OPLA-Pt groups was 172 and 282 days, respectively ($P = .010$).

Infection of the surgical site was a common problem. Infection was diagnosed in 38 dogs (47.5%) and was apparent within 6 months in 13 of these dogs (34.2%). The severity of infection varied from mild to severe. Bacteria cultured from these wounds were often multiple, and a number of different types of bacteria were identified. Oral antibiotics were frequently successful in controlling local wound infections but were rarely curative. Wound debridement, OPLA removal, and implantation of antibiotic-impregnated methylmethacrylate beads was performed in 16 dogs with infections refractory to antibiotic therapy. Infection significantly decreased local recurrence ($P = .031$) and increased survival time ($P = .033$) according to univariate analysis, although multivariate analysis showed that infection was not prognostic for either local recurrence or survival.

Systemic Toxicity

The use of intracavitary OPLA-Pt did not have a significant effect on systemic toxicity. There was no significant difference in bone marrow toxicity ($P = .203$). Mild to marked toxicity was recorded in 34 dogs in the control group (85.0%) and 27 dogs in the OPLA-Pt group (67.5%). There was no significant difference in gastrointestinal toxicity ($P = .502$); mild to marked toxicity was recorded in 12 dogs in both the control group (30.0%) and the OPLA-Pt group (30.0%). There was no significant difference in the incidence or severity of renal toxicity ($P = .149$). Mild and marked renal toxicity was reported in 25 (62.5%) and 4 dogs (10.0%), respectively, from the control group. In comparison, mild renal toxicity was recorded in 18 dogs (45.0%) from the OPLA-Pt group, whereas 10 dogs (25.0%) experienced severe renal toxicity. BUN levels ($P = .027$) were significantly increased in dogs in the OPLA-Pt group, although there were no significant differences in either creatinine levels ($P = .624$) or renal toxicity ($P = .149$). Peripheral neuropathy was not diagnosed in any dog. Serum, drain fluid, and AUC of cisplatin were not significantly associated with the probability of developing bone marrow, gastrointestinal, or renal toxicity.

Prognostic Factors and Outcome

Postoperative outcome was consistent with previous reports of canine OSA.[1,6,25–29,31,39–41] All dogs were targeted to receive four doses of adjunctive intravenous cisplatin. Forty-two dogs completed 4 doses of chemotherapy, 18 were changed from cisplatin to carboplatin because of renal toxicity, and 38 did not complete the projected chemotherapy course because of the development of metastatic or unrelated life-threatening disease. If dogs received fewer than four doses of adjuvant che-

motherapy, they were significantly more likely to develop local recurrence ($P = .024$) and had a significantly shorter survival time ($P = .003$) according to univariate analysis. However, the total number of chemotherapy treatments was not prognostic for local recurrence or survival according to multivariate analysis. Of the 80 dogs, 77 had died and 3 were still alive at the termination of the study. Sixty-two dogs had died as a result of OSA and 15 as a result of other diseases. Distant metastasis was detected in 57 dogs, with metastatic sites including lungs (n = 45), bone (n = 35), and other sites (n = 30), alone or in combination. Survival time was significantly decreased with OSA in the radius ($P = .002$), incomplete surgical margins ($P = .002$), low cisplatin concentration in the active suction drain ($P = .018$), absence of infection ($P = .018$), and fewer than four doses of adjuvant chemotherapy ($P = .005$). However, none of these factors were predictive of survival according to multivariate analysis. The median survival time was not significantly different between treatment groups: 301 days (range, 84–1374 days) in the control group and 280 days (range, 34–1362 days) in the OPLA-Pt group ($P = .300$; Fig. 3).

DISCUSSION

The effect of local chemotherapy was investigated in a randomized, prospective study involving 80 dogs with naturally occurring OSA of the distal radius or ulna treated with limb-sparing surgery. The primary goal was to assess the effect of local chemotherapy on the rate of local tumor recurrence. Local tumor recurrence, rather than survival time, was selected as the end point because euthanasia and survival are subject to owner bias.

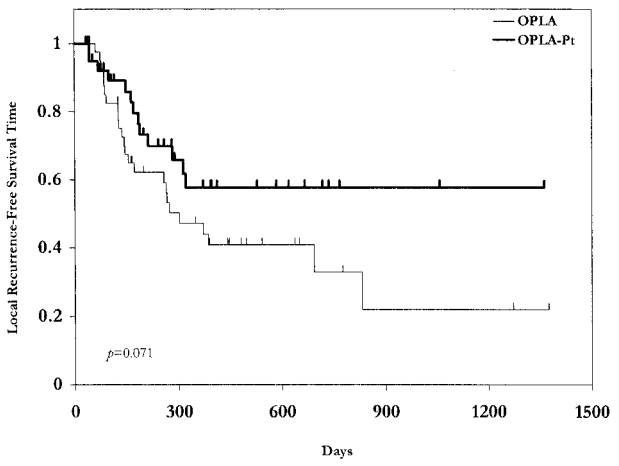

FIG. 3. Kaplan-Meier survival curve for dogs in the control and OPLA-Pt groups.

The use of OPLA-Pt reduced the rate of local recurrence and increased the time to local recurrence after limb-salvage surgery for dogs with OSA. The reduction in the rate of local recurrence with OPLA-Pt was not statistically significant, but a trend was observed ($P = .071$). Furthermore, dogs in the OPLA-Pt group were almost 2 times less likely to develop local recurrence than dogs in the control group. The difference in time to local recurrence was also significant when the control and OPLA-Pt groups were stratified into complete and incomplete surgical resection ($P = .004$). The use of OPLA-Pt is further supported by other experimental and clinical animal models in which the rate of local recurrence is significantly reduced with implantation of OPLA-Pt into the wound bed after resection of various tumors, including mammary carcinomas, cutaneous squamous cell carcinomas, oral melanomas, and soft tissue sarcomas.[14,17–20,23]

A secondary aim of the study was to evaluate the presence and severity of systemic toxicity associated with the use of OPLA-Pt. There were no significant differences between the control and OPLA-Pt groups in bone marrow and gastrointestinal toxicity. In dogs with OPLA-Pt, there was a significantly increased concentration of BUN and a disproportionate but nonsignificant number of dogs with severe renal toxicity. Cisplatin, the active chemotherapeutic compound in OPLA, is a potent nephrotoxic agent, and an aggressive diuresis protocol is recommended with the systemic administration of cisplatin to minimize nephrotoxicity.[34–36] The in vivo elution characteristics of cisplatin from OPLA-Pt are not completely known, although 80% of total cisplatin is released in the first 21 days.[23] Nephrotoxicity may occur if a high concentration of cisplatin is rapidly eluted without appropriate diuresis. However, despite the differences in BUN, there were no significant differences in either serum creatinine levels or renal toxicity between treatment groups, and these findings are supported by previous studies that have shown a low risk of nephrotoxicity, even with OPLA-Pt doses exceeding the maximum systemic canine dose of 70 mg/m^2.[16,30]

The final aim of this study was to identify prognostic factors associated with local recurrence and survival in dogs with appendicular OSA treated with limb-sparing surgery. These included surgical margins, postoperative infection, and adjuvant chemotherapy. The completeness of surgical resection had a significant correlation with local recurrence and survival independent of the use of OPLA-Pt. Incomplete resection, which occurred in approximately half the dogs from each group, resulted in a significantly increased risk of local recurrence on univariate and multivariate analysis. Survival time was

significantly decreased after incomplete resection on univariate, but not multivariate, analysis, even though the 6- and 12-month survival rates for dogs with complete resection were 155% to 236% greater than for dogs with incomplete resection. Local recurrence may negatively influence survival in dogs[5] and humans[13] with appendicular OSA; however, Straw and Withrow[4] showed that local recurrence does not affect survival and that locally recurrent tumors can be managed by using techniques similar to those used for primary bone tumors, such as limb-sparing surgery, amputation, and palliative radiotherapy. The incidence of incomplete surgical resection after limb-sparing surgery has since been decreased by the use of imaging modalities, such as nuclear scintigraphy, computed tomography, and magnetic resonance,[1,42,43] to provide a more accurate estimation of osseous margins and by a more aggressive surgical approach.

Infection of the surgical site was frequent. It occurred in 48% of dogs, and two thirds were diagnosed >6 months after surgery. OPLA is unlikely to have contributed to postoperative infection, because the biodegradable carrier was sterilized with gamma radiation before implantation. Infection is a well-recognized and common problem in human and canine limb-sparing surgery, especially with the use of massive allografts.[1,4,6–8,10,12,38] The causes are unknown, although hypotheses include extensive soft tissue resection, poor soft tissue coverage, implantation of a large segment of nonvascularized cortical bone, and immunosuppression resulting from neoplasia and systemic chemotherapy.[1,38] In this study, univariate analysis showed that infection significantly decreased the rate of local recurrence and increased the survival time. However, according to multivariate analysis, infection was not prognostic for either local recurrence or survival time. In contrast, a recent retrospective analysis of dogs with appendicular OSA treated with either amputation or limb-sparing surgery showed that dogs with infected limb–sparing surgery had a significantly longer disease-free interval and survival time compared with non–infected limb–sparing surgery and amputation.[41] The relationship between infection and improved outcome is not fully understood and is currently being investigated.

Adjuvant chemotherapy has significantly improved the survival time of humans and dogs with appendicular OSA.[1,11,12,24–29,31,39,40] All dogs in this study were targeted to receive four doses of adjuvant cisplatin beginning 3 weeks after surgery and at 3-weekly intervals. The timing of the first dose of chemotherapy has no significant association with metastasis or survival in dogs.[27,39] Furthermore, there is no apparent survival advantage between single- and multiple-agent chemotherapy protocols in dogs.[1,24–27,29,31,39,40] Thirty-eight dogs did not complete the projected chemotherapy course because of development of metastatic disease or unrelated life-threatening conditions. Failure to receive four doses of chemotherapy resulted in a significantly increased risk of local recurrence and decreased survival time on univariate analysis. However, the total number of adjuvant chemotherapy doses was not prognostic for either local recurrence or survival on multivariate analysis.

The biologic behavior and survival outcome for dogs with appendicular OSA in this study were similar to those in previous studies.[1,2,4–6,24–29,31,39,40] The median survival times for dogs in the control and OPLA-Pt groups were not significantly different: 301 and 280 days, respectively. This is similar to previous reports[6,24–29,31,39,40] with a median survival time ranging between 262 and 413 days for dogs with appendicular OSA managed with either amputation or limb-sparing surgery and adjuvant chemotherapy. In accordance with other retrospective analyses,[2,5,6,24–29,31,39,40] metastatic disease was eventually diagnosed in 71% of dogs in this study, and the most common metastatic sites were lungs and bone.

Limitations of this study included the blinding procedure and degree of censorship. Surgeons were the only investigators blinded to the use of OPLA or OPLA-Pt to avoid the biased and nonrandomized implantation of OPLA-Pt in dogs with known incomplete resection. A high number of dogs were censored from analysis, especially in the OPLA-Pt group, because of death from unrelated causes or disease-related death before the expected development of local recurrence. Censorship decreased the volume and power of statistical analysis and may have negatively affected the degree of significance between groups, especially in terms of the rate and time to local recurrence. Finally, univariate analyses suggested that a number of variables, such as completeness of resection and infection, were significantly associated with outcome. However, few of these variables remained significant on multivariate analysis because confounding between levels of various prognostic factors limited the ability to assess any single variable independently of other factors.

CONCLUSION

Although not statistically significant, the results of this study support the hypothesis that OPLA-Pt reduces the rate of local recurrence after limb-sparing surgery in dogs. Furthermore, systemic toxicity associated with cisplatin release from OPLA-Pt is minimal. Complete surgical resection, postoperative infection, and completion

of the targeted adjuvant chemotherapy protocol had a significant correlation with local recurrence and survival on univariate analysis. However, on multivariate analysis, the only prognostic factor for local recurrence was incomplete surgical resection, and no prognostic factors were identified for survival.

ACKNOWLEDGMENTS

The acknowledgments are available online in the full-text version at www.annalssurgicaloncology.org. They are not available in the PDF version.

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