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Objective—To characterize clinical and pathological features of implant-associated neoplasms in dogs.

Design—Retrospective case-control study.

Animals—16 dogs with implant-associated neoplasia and 32 control dogs with osteosarcoma without implants.

Procedures—Medical records of dogs with tumors associated with metallic implants (cases) treated between 1983 and 2013 were reviewed. Two dogs with naturally occurring osteosarcoma (controls) were matched to each case on the basis of tumor location, age, and sex.

Results—Median time from implant placement to diagnosis of neoplasia was 5.5 years (range, 9 months to 10 years). Pelvic limbs were most frequently affected, including the tibia (8/16) and femur (5/16), with 1 neoplasm involving both the femur and pelvis. Implant-associated tumors most commonly affected the diaphysis (15/16), with osteosarcomas significantly more likely to involve the long bone diaphysis in case dogs than in control dogs with naturally occurring osteosarcomas. Osteosarcoma was the most common tumor, accounting for 13 of 16 implant-associated tumors. For 7 of these osteosarcoma cases, review of histopathology results enabled subclassification into osteoblastic nonproductive (n = 3), chondroblastic (2), osteoblastic productive (1), and fibroblastic (1) groups. Three case dogs had a diagnosis of histiocytic sarcoma, fibrosarcoma, and spindle cell sarcoma.

Conclusions and Clinical Relevance—Results of this study highlighted important anatomic differences between spontaneous and implant-associated neoplasia in dogs. (J Am Vet Med Assoc 2015;247:778–785)
Materials and Methods

Case selection criteria—An electronic medical records database was used to retrospectively review medical records for dogs with implant-associated neoplasia treated at the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California-Davis between January 1, 1983, and January 1, 2013.

Cases were included if a diagnosis of neoplasia was confirmed by means of histopathologic or cytologic assessment of tissue samples and if a radiographic report was available describing the tumor to be located in direct contact with any type of metallic surgical implant. Exclusion criteria were the lack of a definitive diagnosis on the basis of histopathology, cytology, or both; and lack of a radiology report confirming the location of the tumor.

Medical records review—Histopathologic features were reviewed, when available, on archived slides stained with H&E and were evaluated in a blinded fashion by a single board-certified veterinary anatomic pathologist (BGM). Cytologic smears were also reviewed, when available, on archived slides stained with Wright-Giemsa, as well as cytochemical stains, as available, by a single board-certified veterinary clinical pathologist blinded to case data and diagnosis (WV). Radiographs, when available, were reviewed in a blinded manner by a single board-certified veterinary radiologist (EGJ). Radiographic location of the tumor was evaluated, as defined by previously reported recommendations. For the purposes of anatomic localization within the appendicular skeleton, the following anatomic locations were defined: the epiphysis extended from the physeal plate to the subchondral bone underlying the articular cartilage; the metaphysis was defined as the flared end of the bone lying between the physeal plate and uniform-diameter bone shaft (diaphysis); and the diaphysis comprised the midshaft, uniform-diameter region of the long bone between the proximal and distal metaphyses.

To investigate differences between implant-associated tumors and naturally occurring variants, control cases were extracted from the same electronic medical record database. Controls were included if the same tumor was diagnosed via histopathology, if there was no report of trauma or implantation in the affected limb, and if radiographs were available for review. Controls were matched to cases by year, sex, and anatomic location of the tumor. Two controls per case were selected to improve study power and efficiency.

Statistical analyses—Descriptive statistics are reported as median and range. A Fisher exact test was used to determine whether tumor location differed between implant-associated case dogs and control dogs. Statistical analyses were performed with a commercially available program, and \( P < 0.05 \) was considered significant.

Results

Eighteen dogs were identified as potential cases on the basis of the initial medical records search. Two patients were excluded because of the lack of histopathologic or cytologic confirmation of neoplasia, resulting in a total of 16 cases meeting study inclusion criteria. The median age of patients at the time of tumor diagnosis was 8.5 years (range, 3 to 14 years). Breeds included Labrador Retriever (n = 5/16), Pitbull Terrier (3/16), and 1 each of German Shepherd Dog, Australian Shepherd, Golden Retriever, Mastiff, Berger Picard, Bernese Mountain Dog, Rottweiler, and mixed breed (8/16 total). The median body weight was 33 kg (72.6 lb; range, 25.5 to 46.5 kg [56.1 to 102.3 lb]). Seven dogs were spayed females (n = 7/16), 6 were castrated males (6/16), 2 were sexually intact males (2/16), and 1 was a sexually intact female (1/16). Median time from surgical implant placement to diagnosis of neoplasia was 5.3 years (range, 0.75 to 10 years). Implant types included plate and screws (n = 6/16); TPLO plate (3/16); plate, screws, and cerclage wires (2/16); plate, screws, and polymethylmethacrylate (1/16); a total hip replacement (femoral and acetabular prostheses for a cemented total hip system with polymethylmethacrylate; 1/16); and a metal crimp clamp associated with extracapsular cruciate repair (1/16). All TPLO plates were Slocum plates. Complications with healing of the initial fracture and repair were reported in 8 of 16 cases. These included osteomyelitis (n = 4/16), fracture nonunion (2/16), and delayed fracture healing (2/16). It was not determined whether postsurgical complications occurred in 5 cases, and it was specifically noted that no complications were evident in 3 cases. Signalment, implant type, complications, and time interval from implant placement to tumor diagnosis for individual patients were reported (Online Supplement, Table 1; available at avmajournals.avma.org/toj/avn/247/7).

Radiography—Radiographs of the tumor, obtained at the time of diagnosis, were available for review in 7 dogs. In 1 dog that underwent a total hip replacement, a mixed productive and destructive, but primarily destructive, lesion affected both the proximal portion of the femur and pelvis and appeared to involve surrounding soft tissues. Plates and screws were implanted in 2 dogs. In the first dog, an expansile, mixed productive-destructive, predominantly destructive, mid-diaphyseal mass was centered under a bone plate. In the second dog, a primarily destructive, minimally productive lesion was centered around the bone plate. A mixed productive-destructive, predominantly productive lesion was centered around the distal aspect of a TPLO plate in the proximal portion of the diaphysis in 1 dog. In 2 further cases of tumors around TPLO plates, one tumor was centered under the implant and was a destructive lesion affecting the proximal portion of the diaphysis (Figure 1), whereas the other tumor was a mixed productive-destructive lesion centered around the plate and confined to the proximal diaphysis. Considerable external and endocortical lysis as well as soft tissue swelling accompanied the second tumor. An area of mixed lytic and productive change was seen around a metal crimp clamp in the tibial metaphysis of 1 dog.

Seven dogs had thoracic radiographs obtained at the time of tumor diagnosis available for review. No evidence of metastatic disease was seen on any of the thoracic radiographs reviewed; however, 5 dogs had reported metastatic disease.

Pathology—A definitive diagnosis was achieved by reviewing the histopathologic features alone in 8 of 16 dogs.
events; histopathology in conjunction with cytology in 4 of 16 cases; cytology, cytochemical analysis, and immunocytochemical analysis in 3 of 16 cases; and the cytologic features alone in 1 case. Where both histopathology and cytology were available, the cytologic diagnoses agreed with the histopathologic diagnoses in all 4 cases. Slides from 9 dogs assigned a definitive diagnosis on the basis of results of histopathologic examination, and all the cytology and cytochemical slides were available for review.

Thirteen of 16 patients had a diagnosis of OSA, with single diagnoses of histiocytic sarcoma, fibrosarcoma, and spindle cell sarcoma. Of the 13 OSAs, 7 cases with histopathology available for review were subclassified as osteoblastic nonproductive (n=3/7), osteoblastic productive (1/7), fibroblastic (1/7), chondroblastic (1/7), and mixed (chondroblastic, osteoblastic, and fibroblastic; 1/7).

Most tumors affected the diaphysis of long bones (n=15/16). Tumors affected the diaphysis only in 13 of 16 cases, whereas 1 of 16 affected the diaphysis, metaphysis, and epiphysis; 1 of 16 involved the diaphysis and metaphysis; and 1 of 16 was confined to the metaphysis. When cases of OSA were investigated (n=13), there was a significant (P<0.001) difference in tumor location between cases and controls, with implant-associated OSAs more likely to affect the long bone diaphysis, with only 1 of the 26 control cases found in the distal portion of the diaphysis and all others located in the metaphyseal region. Tumors occurred most frequently in the pelvic limbs (n=14/16), including the tibia (8/16), femur (5/16), and both the femur and pelvis (1/16). Two tumors occurred in the radius (n=2/16).

Gross appearance—On gross examination, the size of the tumors (when documented) at their largest dimension ranged from 4 to 15 cm (median, 9.25 cm). Gross descriptions of the tumors were available in 7 cases. In 1 dog, an 11.8-cm-long metallic plate was present on the lateral aspect of the distal portion of the femur and was held in place with 7 screws. On sagittal section, the distal end of the femoral diaphysis widened from 2.5 cm to 3.9 cm, and the medullary cavity was replaced by soft, white tissue. The tibia in another dog had an attached 11-hole metallic plate and screws associated with a single cerclage wire, with surrounding soft tissues completely encased in friable, white to pink proliferative tissue that exuded pink fluid on section. One case had a 7 × 7.5 × 15-cm, firm, multilobulated, white to light tan mass surrounding the left femoral diaphysis, adjacent to an attached 1-cm-wide × 6-cm-long metallic plate. Locally extensive regions of periosteal bone formation were associated with the plate. In another dog, a 4-cm-diameter, raised mass distorted the craniodistal aspect of the femur. On transverse sectioning of the distal portion of the femur, the cut surface was mottled beige to dark brown, with numerous small visible fracture lines and a lack of distinction between cortical and trabecular bone. Sagittal sectioning of the femur revealed two-thirds of the medullary space effaced by soft to hard, white or tan to brown mottled tissue that was smooth and glistening. A poorly delineated mass, measuring 8.5 × 3.5 × 2 cm, distorted the distal portion of the radius and partially surrounded a metallic bone plate attached to the bone with both screws and polymethylmethacrylate resin in 1 case. In another dog, there was a lytic and proliferative mass associated with proliferative periosteum affecting the proximal portion of the tibia. The proliferative lesion partially surrounded a TPLO plate that had been removed by the submitting clinician prior to submission of the limb to the pathology service. The mass measured 10 × 6 × 4 cm and distorted the cortical and medullar surfaces of the proximal portion of the tibia, accompanied by a markedly raised periosteum. At least 3 screw tracts, with prominent adjacent fibrosis, penetrated through the tibial bone at the site of the previously removed TPLO plate (Figure 1). Finally, a firm mottled tan to dark brown mass extended through the proximal portion of the tibia to the caudal cortex in 1 dog. Periosteal proliferation up to 0.9 cm thick extended medially and laterally on the cranial as-

Figure 1—Gross and radiographic appearance of an implant-associated OSA in the tibia of an 8-year-old spayed female Pitbull Terrier. The patient had undergone TPLO 7 years previously. A—The medial and dorsal aspects of the proximal portion of the tibia are distorted by a proliferative mass. Note the multiple screw holes present after removal of a TPLO plate (arrows). Bar = 1 cm. B—A destructive lesion is centered under a TPLO plate, lifting the periosteum of the proximal portion of the tibia.
pect of the tibia, with degenerative changes affecting the proximal articular surface of the tibia and osseous proliferation of the femur-associated fabella (sesamoid bone).

**Histopathology**—Nine cases had histopathology slides available for review. Three tumors were diagnosed as osteoblastic nonproductive OSA. These tumors were composed of dense sheets of polyhedral to spindloid neoplastic cells with small amounts of interspersed, extracellular, poorly delineated, eosinophilic, tumor-associated osteoidal matrix. The neoplastic cells had moderate amounts of amphophilic cytoplasm and round, hyperchromatic nuclei with finely stippled chromatin. Anisocytosis and anisokaryosis were marked, and mitotic figures averaged 1 to 5/400 X hpf. Scattered multinucleated giant cells were evident. All these OSAs demonstrated variable amounts of necrosis.

Two chondroblastic OSAs demonstrated densely cellular aggregates of neoplastic cells with small amounts of lacy eosinophilic, extracellular, tumor-associated osteoidal matrix and frequent large irregular islands of variably distinct basophilic cartilaginous matrix multifocally embedded with neoplastic cells. Neoplastic cells were spindloid to polygonal with small amounts of eosinophilic cytoplasm and round to ovoid nuclei. Cells embedded within the islands of cartilage matrix were situated within irregularly sized lacunae, with mostly 1 and rarely 2 cells/lacuna. Anisocytosis and anisokaryosis were marked, and mitotic figures ranged from 1 to 3/400 X hpf.

Single fibroblastic and osteoblastic variants of OSA were also identified. The fibroblastic OSA was highly cellular with streams of neoplastic cells arranged in parallel bundles and fascicles forming an undulating chevron pattern. Multifocally, small amounts of eosinophilic, tumor-associated osteoidal matrix were present, intimately associated with individual neoplastic cells. Neoplastic cells were spindloid to pleomorphic with variable amounts of eosinophilic cytoplasm and ovoid nuclei with indistinct nucleoli. Mitotic figures averaged 4/400 X hpf. The osteoblastic productive OSA was highly cellular, with neoplastic cells arranged in both streams and bundles associated with a prominent extracellular lattice of eosinophilic, variably cross-linking, organized trabeculae of tumor-associated osteoidal matrix (Figure 2). Neoplastic cells were spindloid to pleomorphic with marked anisocytosis and anisokaryosis and 1 or 2 mitotic figures/400 X hpf. The neoplastic population was interspersed with numerous multinucleated giant cells. Multiple large regions of necrosis were evident.

The fibrosarcoma was highly cellular with elongated spindloid cells arranged in regular orthogonal bundles. Extracellular matrix was not evident. Neoplastic cells had a scant amount of cytoplasm and ovoid nuclei with finely stippled chromatin. Mitoses averaged 0 to 1/400 X hpf, large regions of necrosis and areas of bone lysis were common.

Finally, a spindle cell sarcoma was diagnosed in 1 dog < 1 year after internal fixation. The tumor was highly cellular with spindle-shaped neoplastic cells organized into interlacing sheets and bundles embedded within a collagenous connective tissue stroma. Tumor cells had a small amount of eosinophilic cytoplasm with indistinct cell borders and ovoid to cigar-shaped nuclei. Anisocytosis and anisokaryosis were moderate, and 1 to 5 mitotic figures/400 X hpf were seen. Rare multinucleate giant cells were also noted. For this tumor, immunohistochemical staining was available for review. Tumor cells demonstrated strong immunopositivity for vimentin and variable immunopositivity for both smooth muscle actin and desmin antigen expression. The initial interpretation was leiomyosarcoma; however, on review, the variable immunopositivity led to the more generic diagnosis of spindle cell tumor, with differential diagnoses including leiomyosarcoma and fibrosarcoma.

Although the control samples were not rereviewed, no histopathologic differences were noted between implant-associated tumors and spontaneously occurring variants on the basis of the experience of the reviewing anatomic pathologist (BGM).

![Figure 2](https://example.com/figure2.png)
Cytology—Slides from all 4 cases for which a diagnosis was based on cytology alone were available for review; 3 of these had concurrent cytochemical analysis performed. Slides from 3 of the 4 cases in which cytology was performed and the diagnosis was confirmed by means of histopathologic examination were reviewed. Four OSAs were highly cellular with a medium to markedly dense pink stippled background. Nucleated cells were distributed individually and in crowded aggregates, often intimately associated with bright pink fibrillar material consistent with extracellular matrix (Figure 2). Neoplastic cells were spindloid to oval to round with low to moderate amounts of medium blue cytoplasm that frequently contained fine pink intracytoplasmic granules and, rarely, clear punctate vacuoles. Nuclei were often eccentric in the round to ovoid cells, and anisocytosis and anisokaryosis were marked with many large, giant tumor cells noted. The third OSA was cytologically similar to those previously described, but also contained large amorphous pools of bright purple material, interpreted as chondroid. Cytochemical staining with alkaline phosphatase was performed in 2 of the OSAs, with strong cytoplasmic positivity in both instances.31

The histiocytic sarcoma was highly cellular with large, individual round to polygonal cells that had abundant cytoplasm, frequently containing coarse, clear vacuoles. Nuclei were round with irregularly clumped chromatin and multiple prominent, variably sized nucleoli. Multinucleation was frequently seen. Anisocytosis and anisokaryosis were marked, and nucleocytoplasmic ratios were variable. Immunocytochemically, these cells had strong cytoplasmic expression of vimentin and variably strong expression of CD1.32

Metastasis—Five of 16 patients had evidence of metastatic disease at the time of tumor diagnosis. Four of these 5 patients had evidence of pulmonary metastasis on thoracic radiographs obtained at the time of tumor diagnosis, though none of these radiographs were available for review. One additional patient had evidence of lymphadenopathy on abdominal ultrasonography, with cytopathologic confirmation of metastatic neoplasia (OSA). Nuclear scintigraphy was performed in only 2 patients. Radiopharmaceutical uptake was confined to the regions of the implant-associated tumors, indicating that these were primary tumors with no evidence of osseous metastases. Nine of the 32 control patients had evidence of metastatic disease at the time of tumor diagnosis. Seven of these control cases had OSA, and 1 each had fibrosarcoma and histiocytic sarcoma.

Treatment and outcome—Three patients were euthanized immediately after the diagnosis was obtained, and a further 3 patients were not treated and were lost to follow-up. The remaining 10 patients underwent amputation of the affected limb (9 OSAs and 1 fibrosarcoma), with 5 of these patients (all OSA) also receiving additional chemotherapeutic regimens including carboplatin (n = 2), Adriamycin (n = 2), and Adriamycin with cisplatin (1). The patient with fibrosarcoma died of an unrelated disease process 3 years after amputation. Three of the 5 patients treated with amputation and chemotherapy were lost to follow-up 5, 5, and 9 months after diagnosis, with another patient euthanized 7 months after diagnosis because of deterioration and progression of metastatic disease. One patient was alive at the completion of the study, 2.5 years after amputation and commencement of chemotherapy. Metastatic disease was evident in this patient on thoracic radiographs 1.5 years after amputation. The remaining patients treated with amputation alone were all lost to follow-up after their surgical procedure. Tumor type, location, and histopathologic features for individual patients were reported (Online Supplement, eTable 2; available at avmajournals.avma.org/toc/javma/247/7).

Discussion

The development of malignancy in association with orthopedic implants is a rare but well-documented complication in veterinary1–3 and human patients.4–6 In the present study, implant-associated tumors in all 16 patients were found to be sarcomas. Osteosarcoma was the most common implant-associated tumor, most frequently affecting the femoral or tibial diaphysis. Osteosarcomas represent 2% to 5% of all malignancies in dogs and are the most common primary tumor of bone in dogs, accounting for up to 85% of malignancies originating in the skeleton.25,36–38 In dogs, spontaneously occurring OSAs tend to arise from the metaphyseal region of long bones. Of 422 spontaneously occurring OSAs in dogs from multiple studies, 95% were located in the metaphysis, whereas the vast majority of implant-associated OSAs in the present study were found to affect the diaphyseal region. When compared with a control population of patients with naturally occurring OSAs in the present study, implant-associated tumors were significantly more likely to be located in the diaphysis of long bones. Most of the cases treated with TPLO plates in the present study, which span the metaphyseal and proximal diaphyseal regions, had tumors confined radiographically to the proximal portion of the diaphysis, affecting only the distal aspect of the bone plate. This was an important difference in anatomic location between spontaneous and implant-associated OSA, supporting the association between the presence of an implant and tumor formation.

Primary tumors in other parts of the body can metastasize to the diaphysis of long bones. To help rule out this possibility, 2 dogs in this series underwent nuclear scintigraphy, revealing no evidence of bone metastases, with only the primary tumor detected. It is also noteworthy that only 4 of 16 cases had evidence of metastasis on thoracic radiography at the time of diagnosis, although results of thoracic radiography were available for only 7 of 16 cases, and 1 additional dog had metastatic disease on the basis of abdominal ultrasonography and cytopathologic examination at the time of diagnosis. These data support the supposition that these tumors represent primary neoplasms and not metastatic disease.

In this study, the predominance of implant-associated OSA mirrors that of previous reports. For 72
implant-associated neoplasms in dogs found in the English-language literature, 63 (87.5%) were diagnosed as OSA.1–4,14–28 Other implant-associated neoplasms previously reported in dogs included undifferentiated sarcoma (n = 4), fibrosarcoma (1), histiocytic sarcoma (1), and malignant mesenchymoma (1). Two cases of lymphoma associated with surgical implants have been reported in human patients.3,20 No histopathologic or cytologic differences between implant-associated neoplasms and spontaneously occurring variants were seen in this series. Interestingly, mixed inflammation and particulate material consistent with metallic debris has been seen in H&E-stained histologic sections from 8 dogs with previously placed TPLO plates, 1 of which had an accompanying poorly differentiated sarcoma,13 a finding not mirrored in the present study. With the exception of location, the radiographic findings associated with implant-associated bone tumors and spontaneously occurring primary bone tumors in the present study were similar. In an experimental study21 in rats evaluating the development of sarcomas associated with various implanted biomaterials, no association was identified between morphology of the sarcoma and the type of biomaterial implanted.

Although it is difficult to ascribe a definitive link between implanted biomaterials and tumor development, there is growing evidence in the literature to suggest that malignancy is a rare complication of the use of such materials. In 1 study1 of OSA in dogs, 12 of 264 (4.5%) dogs had tumors identified in bones with previous fractures, 7 of which were treated with surgical implants. In another study23 of 130 fractures in dogs, 5 (3.8%) OSAs were identified at the site of fracture, all of which were repaired with surgical implants. Large-breed dogs are predisposed to the occurrence of naturally occurring OSA, and most implant-associated bone tumors have been reported in these breeds, a finding mirrored in the present study.30 Very few implant-associated bone tumors have been reported in small-breed dogs or cats.2,24,60 The rarity of implant-associated osseous malignancies and their tendency to occur in large-breed dogs raise the possibility of fracture and subsequent implant placement being coincidental in development of the tumors (ie, association without causality). In a case-controlled study,41 no significant difference was found between metal implants and tumor development; however, all tumors, not only those of bone and surrounding soft tissue, were investigated, and controls were not matched to tumor type. The important difference in anatomic location (metaphyseal vs diaphyseal) for naturally occurring OSAs and implant-associated tumors has been noted. In addition, the bone most commonly affected appears to differ between spontaneous and fracture-associated OSA. Almost half of previously reported fracture-associated sarcomas affected the femur (39/72 [49%]),23 which is a less common location for spontaneous OSAs (87/422 [21%]),23,24,26 which more commonly affect the thoracic limbs. This finding was confirmed in the present study, with implant-associated tumors most frequently noted in the pelvic limbs, most commonly in the femur and tibia. This may be influenced by the relative frequency of pelvic limb fractures versus other bones or by the type of fixation device used. In contrast to previous reports, no tumors were associated with intramedullary pins or external fixators; however, this may also reflect individual surgeon preference for particular implant types.

Many initiating factors have been hypothesized to play a role in the development of implant-associated sarcomas. Investigators have shown that many implant materials, including commonly used stainless steel and titanium, have potential carcinogenic properties.10,11 Corrosion products from metallic implants have been associated with malignancy, and corrosion has been seen in more than 75% of stainless steel components in human retrieval studies.49,45 Additionally, in human patients, chromosomal aberrations have been observed in hematopoietic cells adjacent to implants used in hip arthroplasty procedures.49 Other reported hypotheses for the development of implant-associated sarcomas include tissue damage from the initial trauma, osteomyelitis, or both, which imply that the metallic implants may be associated with but not causally linked to the occurrence of these tumors.47 A common feature of many such cases is a disturbed healing pattern, such as delayed bone unions or nonunions.3,24,26 It is interesting to note that 8 of 16 cases in the present study had reported complications with bone healing after surgical implant placement. Although it was noted in 2 cases that there were no complications around the time of implant placement and recovery, the retrospective nature of this study makes it impossible to determine whether the remaining cases may also have had complications with healing, as the absence of this in the record does not exclude the possibility of altered healing. It is also interesting that in 1 dog, the OSA affected both the femur and the pelvis. Because OSAs do not commonly cross joint spaces, the presence of implanted material in both of these bones with a lesser soft tissue component might also support the possibility of implanted biomaterials in the underlying etiology of such tumors; however, a primary soft tissue OSA invading the bone adjacent to both implants cannot be excluded entirely.

Sarcomas have previously been reported to occur in proximity to TPLO plates, with an increased incidence noted for the Slocum plate and only a single report of a non-Slocum TPLO plate.33,35,36,48 Metal corrosion has been implicated for the apparent increased incidence of Slocum plate-associated neoplasia, although the reported incidence and risk appear variable, from 0.073% incidence4 to a 7-fold risk of developing neoplasia.28 All TPLO plates in the present study were Slocum plates. It is important to note that implant-associated neoplasia has been reported with non-Slocum plates35 and was seen around a metal crimp clamp from an extracapsular repair for 1 case in the present study; this was the first reported case of implant-associated neoplasia with this type of implant.

Radiographs of the original fracture were not available for review in this study; and although unlikely, it is possible that fractures resulting from preexisting lesions (ie, bone tumor–induced pathological fracture) may have been subsequently repaired and not recognized at the time as a pathological fracture. We consider this scenario highly improbable given that the median
time of tumor development after implant placement was 5.5 years (range, 9 months to 10 years) and median survival time for dogs with OSA treated with amputation is 175 days. Even the dog with the shortest time interval from tumor development after implant placement (9 months), with no evidence of pulmonary metastases or treatment, were well outside this expected progression of disease.

Results of the present study suggested that a definitive biopsy-based diagnosis is important in view of the disparate treatment recommendations and prognosis for implant-associated tumors and additional potential complications of surgical implant placement such as osteomyelitis and delayed bone healing. The specific tumor diagnosis within the category of implant-associated neoplasia also affects prognosis and treatment. For example, the patient with fibrosarcoma in the present case series died of an unrelated disease process 3 years after amputation. Other tumors diagnosed in this study, such as OSA or histiocytic sarcoma, are generally not associated with such prolonged survival times.

Although the present study was small, we suggest that prognosis did not appear to differ for dogs with implant-associated OSA versus those with naturally occurring disease. Several limitations of this study related to its retrospective nature. Archived histopathology slides were available for review in 9 of 12 cases. Given that the interpretation of 1 case differed (albeit slightly) between the original diagnosis and the review, it is possible that other tumors not available for review may have been interpreted differently. However, we considered this unlikely given that there was agreement for all OSA cases and that the 3 cases in which histopathology was not available were originally interpreted as OSAs.

Diagnosis was based on cytologic analysis with cytochemical analysis in 3 cases and cytology alone in 1 case. Osteosarcoma was diagnosed on the basis of the characteristic cytologic appearance and strong cytoplasmic alkaline phosphatase staining in 2 cases. The utility of alkaline phosphatase staining in cytologic specimens has previously been investigated with a sensitivity and specificity of 100% and 89%, respectively. In that study, positive results were rarely seen in tumors other than OSA, including 1 multilobular tumor of bone, 1 amelanotic melanoma, and 1 chondrosarcoma. Notably, 3 of 4 chondrosarcomas were negative for alkaline phosphatase staining. With the characteristic cytomorphology as well as the positive alkaline phosphatase staining, the cytologic diagnosis of OSA is considered reliable. One of the cytology cases reviewed in the present study did not have concurrent cytochemical analysis. The diagnosis on the basis of this sample was OSA originally and OSA on review, and the same diagnosis was made on both cytology and histopathology in cases where both were available. The histiocytic sarcoma had a classic cytologic appearance and strong cytoplasmic CD1 expression, consistent with this diagnosis. Finally, although the general type of metallic implant used could be determined for each case, retrospective information on the composition and specific type of implant metals was not available, except for TPLO plates, and hence no conclusions on effect of the specific metal alloy can be drawn.

Cumulative clinical and scientific evidence supports the concept of implanted biomaterials contributing to the development of malignancies. Although rare, this phenomenon may represent a serious potential complication in such patients. The anatomic location of these sarcomas in the long bones, predominating in the diaphyseal region, may be helpful to alert practitioners to the possibility of implant-associated neoplasia in these patients. On the basis of our results, as well as those of prior studies, further research is warranted to evaluate the hypothesis that implanted biomaterials can result in tumor development.

References