Bi-institutional retrospective cohort study evaluating the incidence of osteosarcoma following tibial plateau levelling osteotomy (2000–2009)

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Keywords
Osteosarcoma, tibial plateau levelling osteotomy, fracture site sarcoma

Summary

Objectives: To evaluate the incidence and risk factors for occurrence of osteosarcoma (OSA) following tibial plateau levelling osteotomy (TPLO).

Methods: Medical records of client-owned dogs that underwent consecutive TPLO procedures at two institutions were retrospectively reviewed. Referring veterinarians and owners were contacted for follow-up. Each institutional cohort was assessed separately, and the incidence density rate and median time to occurrence of OSA at the TPLO site and at other sites were calculated. Marginal Cox regression was used to calculate hazard ratios and 95% confidence intervals for potential risk factors for occurrence of OSA.

Results: There were 472 CLINIC A (Colorado State University Veterinary Teaching Hospital) and 1992 CLINIC B (SAGE Centers for Veterinary Specialty and Emergency Care) TPLO cases with over one year of follow-up available. There were five and six dogs within the cohorts that developed OSA at the site of TPLO, and seven and 22 dogs that developed OSA at other anatomical sites, respectively. The incidence density rates of OSA at the TPLO site were 30.4 and 10.2 per 10,000 dog-years at risk, and other sites were 42.6 and 37.5 per 10,000 dog-years at risk. The median time to occurrence of OSA of TPLO site OSA was 4.6 and 4.4 years, which was longer than that of other site OSA of 2.9 and 3.4 years.

Clinical significance: There is a low incidence of OSA following TPLO surgery. The longer time to occurrence for TPLO site OSA is similar to that for fracture-associated sarcoma, and could indicate a similar underlying pathophysiology rather than spontaneous OSA occurrence.

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Introduction

Implant or fracture-associated sarcomas are a devastating complication of orthopaedic fixation in both dogs and people (1-12). Although postulated to occur rarely, the true incidence of implant or fracture-associated sarcomas remains unknown, but it is thought to represent less than 1–4.5% of all osteosarcoma (OSA) cases in dogs (13, 14). Sporadic reports have described development of sarcoma following tibial plateau levelling osteotomy (TPLO) surgery (14-18). The incidence of the development of neoplasia of the proximal tibia following TPLO was estimated to be 0.075% of 37,082 TPLO cases based on a voluntary survey of veterinarians performing TPLO procedures (19). The incidence of occurrence of neoplasia at sites other than the proximal tibia in dogs following TPLO is unknown. In the general population, OSA has been reported to occur most commonly in the forelimbs, with the proximal humerus and distal radius being most frequently affected (20). An increased risk of OSA has been found with increasing weight, height, and age (21). Certain breeds, including the Irish Wolfhound, Saint Bernard, Great Dane, Greyhound, and Rottweiler, have been identified to be at an increased risk (20, 21).

Several theories have been proposed for mechanisms of development of sarcoma at fracture, implant, or osteotomy sites such as TPLO sites. These include postulation that the presence of the metal implant acts as a nidus for continuing inflammation and

repair, or with complicated fracture healing or infection, there is continuing inflammation and repair with multiple mitoses and subsequent neoplasia development (2). Another proposed theory is that corrosion causes metal debris in the region of the implant, which causes an altered host reaction and disrupted cellular activity, leading to development of cancer (2, 16, 22). In addition, increased concentrations of metals have been found in animal serum, urine, and tissue remote to the site of metallic implants; coupled with the findings that metallic compounds such as chromium, cobalt, and nickel have been found to be oncogenic raises the possibility of surgical implants contributing to malignant transformation elsewhere in the body (2). There has been limited evaluation of the metallurgy of explanted TPLO plates. Concern has been expressed about the material properties and casting process used in the manufacture of TPLO plates, resulting in possible corrosion and adverse biological effects (2, 3). However, a more recent study evaluating the microchemical and surface composition of commercially available TPLO plates did not find evidence of corrosion or substantiate previous concerns about metallurgy (24). Lastly, bone infarction has been postulated to predispose to the development of OSA in dogs implanted with total hip replacements; to the authors' knowledge, this has not been reported in association with the TPLO procedure thus far (25).

Given the prevalence of cranial cruciate ligament disease and popularity of the TPLO procedure for treatment of cranial cruciate ligament rupture, further assessment and characterization of the epidemiology of development of sarcoma at the TPLO and other sites in dogs with a history of TPLO is merited (26). The authors focused on occurrence of OSA, as this is the most commonly occurring primary appendicular bone tumour, and the most common tumour reported in previous publications of TPLO site neoplasia in dogs (14, 15, 18, 27–30).

The primary purpose of the study was to determine the incidence of OSA at the TPLO site and other sites following TPLO surgery in two institutional cohorts of dogs undergoing consecutive TPLO procedures. The secondary aim was to assess potential risk factors for occurrence of OSA at the TPLO site and other sites. We hypothesized that the incidence of OSA at TPLO sites would be low in both cohorts and that complications of infection or fracture following TPLO surgery would increase the risk of occurrence of OSA at the TPLO site.

Materials and methods

Eligibility criteria

An electronic medical records search was performed at Clinic A (Colorado State University Veterinary Teaching Hospital) and Clinic B (SAGE Centers for Veterinary Specialty and Emergency Care) to identify consecutive TPLO procedures performed betweenJanuary 1, 2000 and December 31, 2009. Eligible TPLO procedures could have been performed unilaterally or bilaterally (staged or single session). Tibial plateau levelling osteotomy procedures in dogs of high body weight that utilized an orthopaedic plate in addition to a TPLO-plate to stabilize the osteotomy were included, but procedures where TPLO was performed in combination with other ancillary stifle stabilization procedures, such as an intra-articular graft or extracapsular repair, were excluded. Patients with TPLO procedures with less than one year of follow-up were excluded given the minimum time to occurrence of fracture-associated sarcoma that has been reported is one year (2).

Medical record review

The electronic medical records were evaluated for signalment information at the time of presentation for the TPLO procedure, including date of birth, breed, body weight, sex, and neuter status. Details about each TPLO surgical procedure were recorded, including the date of surgery, laterality of the operated limb, if the procedure was bilateral, manufacturer of the TPLO plate, and if an additional plate was used for osteotomy stabilization. If a dog had bilateral procedures performed, each TPLO procedure was considered as a separate entry to allow description of characteristics of each surgery and any subsequent complications.

Follow-up and outcome

Medical record evaluation was performed between October 31, 2011 and November 1, 2012 for both cohorts. The diagnosis of postoperative infection or fracture involving the operated tibia or fibula, including subclinical tibial crest fractures, at a follow-up visit at any time after surgery was recorded. A clinical definition of postoperative infection was used; the TPLO site was denoted as having a postoperative infection if the dog had a positive bacteriological culture, or in the absence of a bacteriological culture being performed, if there was clinical suspicion of infection and antibiotic medications were prescribed. There was no time limit for detection of infection. A fracture was recorded if a fracture was diagnosed on radiographs in the postoperative period. The absence of documentation of TPLO site infection or fracture was classified as an absence of these complications for the analysis. The medical records were evaluated for evidence of diagnosis of OSA at the TPLO site or at other sites. The term "other site OSA" will be used to denote occurrence of OSA at a site other than the proximal tibia of a tibia that underwent a TPLO procedure. Diagnosis of OSA was made on the basis of histopathology, with or without additional cytology or radiographic findings suggestive of a primary bone tumour. Histopathologic samples at both institutions were always reviewed by a board certified pathologist. Radiographs were always reviewed by a board certified radiologist at Clinic A, but not always at Clinic B, where they were typically reviewed by a board certified small animal surgeon.

A standardized telephone questionnaire was used to obtain additional follow-up from owners and referring veterinarians at Clinic A between February 1, 2012 and May 15, 2012 (▶Supplementary Tables A and B – available online at www.vcot-online.com). The questionnaire contained questions about whether the dog was diagnosed with OSA; if so, the date of diagnosis, the location and how it was diagnosed (histopathology or cytology) were obtained. Information regarding whether the dog was alive or dead, and the date of last contact was obtained. If the dog was

dead, the date of death or euthanasia and the cause of death or reason for euthanasia were recorded if known. If there was no evidence on follow-up of occurrence of OSA, it was assumed that OSA did not develop within the follow-up period identified. The same standardized questionnaire was used at Clinic B (▶Supplementary Tables A and B – available online at www.vcot-online.com) to obtain the same follow-up information from the referring veterinarians through email and fax between February 16, 2012 and August 14, 2012. The owners from Clinic B were not contacted for follow-up due to financial constraints. To assess any bias that could result from differences in follow-up methods, the authors chose to assess the cohorts separately in the statistical analysis to allow assessment of incidence rates at each institution and allow adjustment for any effect of institution on hazard of occurrence of OSA.

Statistical analysis

The study period was chosen as January 1, 2000 to December 31, 2009. The entire population of dogs that underwent TPLO procedures during this time was included. Signalment information was summarized separately for each institutional cohort and compared for differences between the cohorts, separately evaluating all eligible TPLO cases, and those with greater than one year follow-up. Cases were not excluded from analysis if follow-up information was not available through owners or referring veterinarians but greater than one year follow-up was available from records at Clinic A or Clinic B. For continuous variables the data distribution was evaluated graphically to assess normality; if the data were normally distributed, mean ± standard deviation (SD) were used to describe the data, and if non-normally distributed, median and interquartile range (IQR) were used. Categorical signalment and complication variables (fracture and infection) were described separately for each cohort, with frequencies and percentages in frequency tables. The TPLO plate manufacturers were categorized as Slocum[a], Securos[b], Synthes[c], other or unknown.

The median follow-up time and time to occurrence of OSA at the TPLO site or other site were calculated for each cohort using Kaplan-Meier methodology. The incidence density rates (IDR) of OSA occurrence of TPLO site and other sites were calculated for each institutional cohort. For the incidence calculation, the time at risk stopped at the time of diagnosis of OSA. The incidence rates were multiplied by 10,000 for interpretation as the number of dogs developing OSA per 10,000 dog-years at risk (DYAR); DYAR indicates the years that the entire population has been at risk, taking into account the follow-up period for each dog. Standard errors (SE) for rates were calculated by dividing the square root of the number of cases per cohort by the sum of the DYAR for the cohort, then multiplying by 10,000 (31). The 95% confidence intervals (CI) were calculated (± 1.96 SE). For the purpose of the calculation of time to occurrence of OSA and univariable analysis, if a dog had bilateral TPLO performed and developed OSA at a location other than that of the TPLO, the presence of the tumour was assigned to the first TPLO performed. Univariable analysis was performed to identify possible risk factors for occurrence of TPLO site and other sites by using a marginal Cox proportional hazard model, using robust sandwich estimates of SE, with adjustment for institution (32). This model was used to account for clustering of observations (TPLO) and to allow adjustment for institution to control for confounding due to institutional differences including follow-up and TPLO plate preferences. The hazard ratio (HR) and 95% likelihood CI were reported for each cohort. Variables assessed in the univariable analysis were age at the time of the TPLO, breed (purebred versus mixed breed), sex and neuter status, TPLO plate manufacturer, the presence of bilateral TPLO procedures, and the occurrence of fracture or infection. Given the low number of dogs that developed OSA, a multivariable analysis was not performed. Statistical significance was set at $\alpha = 0.05$ and the statistical analysis was performed using a commercially available software package[d].

a Slocum Enterprises, Eugene, OR, USA
b Securos, a division of MWI, Fiskdale, MA, USA
c Synthes Vet, West Chester, PA, USA
d SAS software, Version 9.3: SAS Institute Inc., Cary, NC, USA

Results

There were 650 and 4000 consecutive TPLO procedures performed between January 1, 2000 and December 31, 2009 at Clinic A and Clinic B, respectively. Follow-up of greater than or equal to one-year was available for 472 and 1992 of the TPLO procedures performed at Clinic A and Clinic B, respectively. Characteristics at the time of TPLO surgery for all consecutive TPLO as well as those for TPLO with follow-up of greater or equal to one year are reported for both cohorts (▶Supplementary Table C – available online at www.vcot-online.com). The cohorts (Clinic A: n = 472; Clinic B: n = 1992) with follow-up greater than or equal to one-year were used for the statistical analysis; the median (range) follow-up time was 4.0 (1 – 11.9) years and 3.5 (1 – 10.9) years at Clinic A and Clinic B, respectively. The total follow-up at each institution was 1645.0 DYAR at Clinic A and 5873.5 DYAR at Clinic B.

Overall, characteristics at the time of TPLO surgery were similar in both institutional cohorts with the exception of the proportion of TPLO performed as part of bilateral procedures (Clinic A 35.2% versus Clinic B 46.6%) and the plate manufacturers used. Multiple plate manufacturers were used by both institutions, however, the majority of plates used were manufactured by Slocum (Clinic A 92.2%; Clinic B 60.1%), with Clinic B using a higher proportion of Securos plates (38.5%) compared to Clinic A (0.2%) (▶Table 1). Infection occurred in 4.9% (23/472) of the TPLO at Clinic A and 6.9% (137/1992) of the TPLO at Clinic B. The majority of the dogs diagnosed with infection had a positive bacteriological culture in both cohorts (Clinic A 16/23 [69.6%] and Clinic B 105/137 [76.6 %]).

Osteosarcoma at the TPLO site was diagnosed in five dogs at Clinic A and six dogs at Clinic B. The IDR (95% CI) for OSA at the TPLO site was 30.4 per 10,000 DYAR (3.8, 57.0) and 10.2 per 10,000 DYAR (2.0, 18.4) at Clinic A and Clinic B.

Characteristic at time of TPLO surgery	Clinic A (n = 472)	Clinic B (n = 1992)
Dog age (years) (mean ± SD)	5.0 ± 2.5	5.5 ± 2.7
Dog body weight (kg) (mean ± SD)	37.4 ± 11.9	35.6 ± 11.6
Sex and neuter status (TPLO: n, %):		
Female intact	11 (2.3%)	44 (2.2%)
Female spayed	226 (47.9%)	1090 (54.7%)
Male castrated	224 (47.5%)	811 (40.7%)
Male intact	11 (2.3%)	46 (2.3%)
Unknown	0 (0.0%)	1 (0.1%)
Breed (TPLO: n, %):		
Purebred	379 (80.3%)	1370 (68.8%)
Mixed breed	93 (19.7%)	622 (31.2%)
TPLO unilateral or bilateral (TPLO: n, %):		
Bilateral	166 (35.2%)	1050 (52.7.%)
Unilateral	306 (64.8%)	942 (47.3%)
Plate manufacturer (TPLO: n, %):		
Slocum[a]	435 (92.2%)	1198 (60.1%)
Securos[b]	1 (0.2%)	767 (38.5%)
Synthes[c]	14 (3.0%)	0 (0.0%)
Other	8 (1.7%)	5 (0.3%)
Unknown	14 (3.0%)	22 (1.1%)
Additional plate used for stabilization (TPLO: n, %):	0 (0.0%)	23 (1.2%)
Complications (TPLO: n, %):		
Fracture	21 (4.5%)	72 (3.6%)
Infection	23 (4.9%)	137 (6.9%)

Table 1 Characteristics of the dogs at the time of the tibial plateau levelling osteotomy (TPLO) procedure for 2464 consecutive TPLO procedures with greater than or equal to one year follow-up at two institutions.

Osteosarcoma was seen at other sites in 7 and 22 dogs at Clinic A and Clinic B, respectively (▶Table 2). The IDR (95% CI) was 42.6 per 10,000 DYAR (11.0, 74.1) and 37.5 (21.8, 53.1) at Clinic A and Clinic B, respectively. Proximal tibial lesions were seen in 5/11 (45.4%) dogs diagnosed with OSA from Clinic A and 6/28 (21.4%) from Clinic B. Hindlimb OSA lesions were seen in 8/12 (66.7%) of the dogs diagnosed with OSA from Clinic A and 17/28 (60.7%) from Clinic B.

The median time to occurrence of OSA of the TPLO site was 4.6 years and 4.4 years at Clinic A and Clinic B, respectively. The median time to occurrence of OSA at other sites was 2.9 years and 3.4 years at Clinic A and Clinic B, respectively. After controlling for institution, the older the dog at the time of TPLO, the less likely it was to develop OSA at the TPLO site (HR 0.66 (95% CI: 0.47, 0.90); p = 0.016; ▶Table 3). Purebred dogs were at a significantly higher risk of developing OSA at a site other than the TPLO site (HR 3.87 [1.35, 16.32]; p = 0.026). All OSA cases at the TPLO site in both cohorts had Slocum TPLO plates implanted, thus the risk of occurrence of OSA at the TPLO site was zero with other plate types or manufacturers. Hazard ratios for TPLO plate type or manufacturer for OSA at other sites are presented without 95% CI as these could not be calculated due to a low number of cases developing OSA at other sites following use of TPLO plates from manufacturers other than Slocum (Clinic A: Synthes (n = 1 case); Clinic B: Securos (n = 5) and unknown (n = 1). Dogs with bilateral TPLO procedures were at a significantly lower risk of developing OSA at other sites (HR 0.30 [0.11, 0.71]; p = 0.0093).

Discussion

The IDR of OSA at the TPLO site was low in two institutional cohorts of TPLO procedures performed from 2000–2009, indicating occurrence of OSA at the TPLO site is rare. The institutional cohorts had different characteristics, so were treated separately for the statistical analysis. There were some institutional differences in the IDR, with Clinic A having a higher IDR of OSA at the TPLO site and a larger CI than Clinic B. The difference may represent a truly higher IDR for Clinic A with large CI due to low numbers of cases or a difference resulting from bias due to differential follow-up and loss to follow-up between the cohorts resulting in fewer cases being identified at Clinic B where the follow-up had been carried out via the referring veterinarians only. Alternatively, the difference could result from institutional differences in practice such as preference of TPLO plate manufacturer. Despite the apparent difference in IDR, the degree of overlap of the confidence intervals makes a substantial difference between these IDR unlikely. The generation of two low estimates of incidence in different clinically representative populations supports the *a priori* hypothesis of low incidence of this condition.

A recent Swedish report described the IDR of bone tumours in 400,000 insured dogs as 5.5 cases per 10,000 DYAR; bone tumours involving the tibia or fibula constituted eight percent of these cases (33). The distribution of proximal or distal location within these bones was not presented in this study. The incidences in our study for both OSA at the TPLO site and other sites are higher than the reported IDR in the Swedish study (33). This could be due to population differences between the two studies. For example, the studies involved different geographic regions, a population of entirely insured versus a mix of uninsured and insured dogs, and the general population of dogs versus a majority of large or giant breed dogs whose owners elected to have a TPLO procedure performed at a referral hospital. Given OSA is reported more commonly in large and giant breed dogs, we may expect a higher incidence in a population comprised almost exclusively of this size of dog (27, 29, 30). In addition, the Swedish study excluded dogs older than 10 years, and as the risk of OSA increases with age, this may have resulted in a low reported inci-

Table 2
Sites of occurrence of osteosarcoma.

Site of osteosarcoma	Clinic A (n = 472 TPLO)	Clinic B (n = 1992 TPLO)
TPLO site	5	6
Other sites: Total	7	22
Other sites – Forelimb:	**4**	**9**
Forelimb, unknown bone	0	1
Humerus, diaphysis	1	0
Humerus, proximal	1	1
Humerus, unknown*	0	1
Radius, distal	1	5
Scapula	1	1
Other sites – Hindlimb:	**3**	**11**
Femur, distal	2	4
Femur, proximal	0	1
Pelvis	1	2
Tibia, diaphyseal	0	1
Tibia, distal	0	3
Other sites – Other:	**0**	**2**
Maxilla/nasal	0	1
Rib	0	1

*Unknown if lesion was distal, diaphyseal or proximal.

dence of OSA in comparison to the study reported here (21, 33).

An alternative explanation for the disparate OSA incidences between the Swedish study and the study reported here could be that dogs treated with a TPLO procedure could be at a greater risk of developing OSA (33). The design of this study does not permit assessment of this question directly due to the lack of assessment of incidence rates of OSA in a group of dogs that did not have TPLO performed. However, findings in this study that may indirectly support this hypothesis were the increased hindlimb site distribution and higher proximal tibial proportion of all appendicular OSA cases than would be expected (hindlimb anatomical site 28.9 – 30.7%; proximal tibia 5.7 – 6.1%) (28, 29). Also of interest is that there were no cases of proximal tibial OSA in dogs where OSA occurred at sites other than a TPLO site. Alternative explanations for these findings could include increased recognition of hindlimb lameness associated with a limb having previous surgery and thus bone tumours in this population of dogs due to the prior TPLO surgery and increased owner sensitivity or propensity to return to a surgeon for follow-up when hindlimb lameness occurs.

Follow-up of a year or more was required for inclusion in the study in an effort to exclude dogs that were not at risk for developing OSA at the TPLO site as the time taken to develop (latency period) fracture-associated sarcoma has been reported as one year or greater and TPLO site OSA has been postulated to occur by a similar mechanism (2, 11, 14). The time to occurrence of OSA at the TPLO site was just over four years with a moderate IQR

Table 3
Univariable results occurrence of tibial plateau levelling osteotomy (TPLO) site and other site osteosarcoma (OSA).

	TPLO site OSA (11 cases)		Other site OSA (28 cases)	
Variable	**HR (95% CI)***	**p-value**	**HR (95% CI)***	**p-value**
Age at TPLO	0.66 (0.47, 0.90)	0.016	1.05 (0.90,1.22)	0.38
Breed:				
Purebred	1.82 (0.46, 12.10)	0.43	3.87 (1.35, 16.32)	0.026
Mixed	1.00 (ref)	-	1.00 (ref)	
Sex & neuter status:				
Female intact	0	<0.0001	2.37 (0.37, 8.40)	0.27
Female spayed	1.64 (0.49, 6.31)	0.43	0.60 (0.27, 1.31)	0.20
Male intact	0	<0.0001	0	<0.001
Male castrated	1.0 (ref)	-	1.0 (ref)	
Plate manufacturer:				
Slocum	1.0 (ref)	-	1.0 (ref)	-
Securos	0	<0.0001	0.82	0.69
Synthes	0	<0.0001	18.14	0.01
Other	0	<0.0001	0	<0.001
Unknown	0	<0.0001	2.56	0.37
Bilateral TPLO	3.19 (0.91, 14.69)	0.080	0.30 (0.11, 0.71)	0.0093
Infection	1.60 (0.09, 8.40)	0.65	1.17 (0.19, 3.91)	0.83
Fracture	0	<0.0001	0.97 (0.05, 4.56)	0.96

*Hazard ratios (HR) adjusted for institution. ref: reference; this category acted as the reference for calculation of the hazard ratio.

for both cohorts, the moderate spread of the latency period is probably a result of the low numbers of cases developing OSA. Despite the reasonable median follow-up times of 4.0 and 3.5 years at Clinic A and Clinic B respectively, it is possible that inclusion of dogs with shorter follow-up times could have led to under appreciation of cases of OSA, as these dogs may develop OSA at a later time; conversely, if we had excluded dogs with shorter follow-up (but greater than 1 year) it may have excluded dogs that were at risk of developing OSA and could falsely increase the estimate of incidence. However, based on the median follow-up times and the study findings of low estimates of IDR in two different institutional cohorts, the authors feel that the study results reflect that it is rare to develop OSA at the TPLO site.

The median time to occurrence of OSA at the TPLO site was longer than the time to occurrence of OSA at other sites in both institutional cohorts. This could represent a difference in the aetiology of the two processes, with OSA at the TPLO site being an implant- or fracture-associated sarcoma rather than spontaneous occurrence at the site of the TPLO, and other site OSA representing spontaneous occurrence of OSA in large or giant breed dogs.

The proportion of dogs that developed infection and fracture were similarly low in both cohorts, in agreement with published complications rates for the TPLO procedure (34, 35). Neither fracture nor infection at the TPLO site resulted in a significantly increased hazard of occurrence of OSA at the TPLO site or other sites; in fact, dogs with fractures had a significantly lower hazard of occurrence of OSA at the TPLO site. For fracture and implant-associated sarcoma, it has been hypothesized that slow fracture healing and infection could lead to cellular changes leading to sarcoma formation (2). In these retrospective cohorts it was not possible to evaluate the severity of fracture or infection complication and how significant the associated inflammation would likely to be. Given the low number of cases of OSA, it is possible this could be a type I error.

Increased age at the time of TPLO was associated with a decreased hazard of occurrence of OSA at the TPLO site. This may be supportive of the previously presented hypothesis that TPLO site OSA is a form of implant- or fracture-associated sarcoma, with time to occurrence similar to the latency period reported for fracture or implant-associated sarcoma (mean latency of 3.49 years, range 2 to 8 years) (7, 14). Thus, younger dogs are likely to have a longer remaining lifespan than older dogs at the time of TPLO surgery, allowing time for TPLO site neoplasia to develop.

All dogs that subsequently developed OSA at the TPLO site had Slocum TPLO plates. Dogs that developed OSA at other sites uncommonly had plates other than Slocum TPLO plates, resulting in an expected low hazard for occurrence of OSA of the TPLO site and other sites. This is probably due in part to the TPLO patent that resulted in almost exclusive use of the Slocum TPLO plate until 2006. Our study period ended December 31, 2009, thus, there were only four years of the study involving implants created by other manufacturers (▶Supplementary Tables D and E – available online at www.vcot-online.com). Fewer numbers of other implants placed, coupled with the fact that they were the most recently applied plates, probably contributed to the lack of TPLO site OSA identified associated with manufacturers aside from Slocum. The high hazard of occurrence of other site OSA with Synthes TPLO plates is likely to be the result of relatively low numbers of these plates used combined with the occurrence of one case of OSA, as such this may represent a type I error. Given the long time to occurrence of OSA at the TPLO site, there may be more TPLO site cases identified that are associated with other plate manufacturers over time. Occurrence of OSA at the site of TPLO surgery that used a TPLO plate made by manufacturers other than Slocum has been described indicating that this complication is not unique to the Slocum plate (15). A follow-up of a later cohort, or continued follow-up of the two study cohorts, could assess for differences of incidence rates over time accounting for change in TPLO plate manufacturer. The assessment of possible risk factors was restricted to univariable analysis generating HR; these are crude estimates due to the low number of OSA cases preventing adjustment for variables other than institution.

Limitations of the study reported here include its retrospective nature. Ideally, histological samples would be re-evaluated by one board certified pathologist. Not all of the radiographs were reviewed by a board certified radiologist at Clinic B. Radiographs were not necessarily obtained of the TPLO site at the time of diagnosis of OSA at a different site; therefore, it is possible that there were some cases of subclinical TPLO site OSA with bone metastasis to a different site which were mistakenly diagnosed as a primary OSA at a different site. However, OSA generally behaves aggressively, resulting in lameness and pain that progresses without treatment; it is therefore felt unlikely that a significant number of cases were subclinical. Diagnosis of OSA may have been less than actual incidence of OSA in both groups due to subclinical OSA at the time of follow-up. Optimally, these patients would be followed to death, with survey imaging such as nuclear scintigraphy and histopathology performed at time of death to accurately diagnose all cases of OSA; this was not possible with the retrospective design of the study. There were also limitations in data analysis. For example, for patients undergoing bilateral TPLO procedures, if OSA was diagnosed at a non-TPLO site, the latency was calculated based on the first TPLO performed. This may have resulted in an artificially prolonged latency period. As patient outcomes were assessed via questionnaire, the reported incidences of TPLO site and other site OSA may have been artificially decreased.

Conclusion

Following TPLO surgery, occurrence of osteosarcoma at the TPLO site or other sites is rare. However, osteosarcoma at the TPLO site should be considered as a differential diagnosis in a dog that is presented with hindlimb lameness and having a history of TPLO performed years previously.

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Conflict of interest

None declared.

References

1. Ward J, Thornbury D, Lemons J, et al. Metal-induced sarcoma. A case report and literature review. Clin Orthop Relat Res 1990; 252: 299–306.
2. Stevenson S. Fracture-associated sarcomas. Vet Clin North Am Small Anim Pract 1991; 21: 859-872.
3. Banks W, Morris E, Herron M, et al. Osteogenic sarcoma associated with internal fracture fixation in two dogs. J Am Vet Med Assoc 1975; 167: 166-167.
4. Harrison J, McLain D, Hohn R, et al. Osteosarcoma associated with metallic implants. Report of two cases in dogs. Clin Orthop Relat Res 1976; 116: 253-257.
5. Keel S, Jaffe K, Nielsen P, et al. Orthopaedic implant-related sarcoma: a study of twelve cases. Mod Pathol 2001; 14: 969-977.
6. Knecht C, Priester W. Osteosarcoma in dogs: A study of previous trauma, fracture and fracture fixation. J Am Anim Hosp Assoc 1978; 14: 82–84.
7. Li X, Hom D, Black J, et al. Relationship between metallic implants and cancer: A case-control study in a canine population. Vet Comp Orthop Traumatol 1993; 6: 70–74.
8. Madewell B, Pool R, Leighton R. Osteogenic sarcoma at the site of a chronic nonunion fracture and internal fixation device in a dog. J Am Vet Med Assoc 1977; 171: 187-189.
9. Sinibaldi K, Rosen H, Liu S, et al. Tumors associated with metallic implants in animals. Clin Orthop Relat Res 1976; 118: 257-266.
10. Sinibaldi K, Pugh J, Rosen H, et al. Osteomyelitis and neoplasia associated with use of the Jonas intramedullary splint in small animals. J Am Vet Med Assoc 1982; 181: 885-890.
11. Stevenson S, Hohn R, Pohler O, et al., Fracture-associated sarcoma in the dog. J Am Vet Med Assoc 1982; 180: 1189-1196.
12. Van Bree H, Verschooten F, Hoorens J, et al. Internal fixation of a fractured humerus in a dog and late osteosarcoma development. Vet Rec 1980; 107: 501-502.
13. Knecht CD, Priester WA. Musculoskeletal tumors in dogs. J Am Vet Med Assoc 1978; 172: 72-74.
14. Straw M. What is your diagnosis? Fracture/implant-associated osteosarcoma following TPLO procedures. J Small Anim Pract 2005; 46: 457-459.
15. Atherton MJ, Arthurs G. Osteosarcoma of the tibia 6 years after tibial plateau leveling osteotomy. J Am Anim Hosp Assoc 2012; 48: 188-193.
16. Boudrieau R, McCarthy R, Sisson RJ. Sarcoma of the proximal portion of the tibia in a dog 5.5 years after tibial plateau leveling osteotomy. J Am Vet Med Assoc 2005; 227: 1613-1617.
17. Harasen GL, Simko E. Histiocytic sarcoma of the stifle in a dog with cranial cruciate ligament failure and TPLO treatment. Vet Comp Orthop Traumatol 2008; 21: 375-377.
18. Thompson AM, Bergh MS, Wang C, et al. Tibial plateau levelling osteotomy implant removal: a retrospective analysis of 129 cases. Vet Comp Orthop Traumatol 2011; 24: 450-456.
19. Slocum TD. Incidence of neoplasia with TPLO surgery and Slocum implant. In: Proceedings of the 32nd Annual Conference Veterinary Orthopedic Society. 2005 March 5-12; Snowmass, CO, USA. pg. 16.
20. Rosenberger JA, Pablo NV, Crawford PC. Prevalence of and intrinsic risk factors for appendicular osteosarcoma in dogs: 179 cases (1996–2005). J Am Vet Med Asooc 2007; 231: 1076–1080.
21. Ru G, Terracini B, Glickman LT. Host related risk factors for canine osteosarcoma. Vet J 1998; 156: 31–39.
22. Boudrieau R, McCarthy R, Sprecher C, et al. Material properties of and tissue reaction to the Slocum TPLO plate. Am J Vet Res 2006; 67: 1258-1265.
23. Charles AE, Ness MG. Crevice corrosion of implants recovered after tibial plateau leveling osteotomy in dogs. Vet Surg 2006; 35: 438-444.
24. Lackowski WM, Vasilyeva YB, Crooks RM, et al. Microchemical and surface evaluation of canine tibial plateau leveling osteotomy plates. Am J Vet Res 2007; 68: 908-916.
25. Marcellin-Little DJ, DeYoung DJ, Thrall DE, et al. Osteosarcoma at the site of bone infarction associated with total hip arthroplasty in a dog. Vet Surg 1999; 28: 54–60.
26. Witsberger TH, Villamil JA, Schultz LG, et al. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc 2008; 232: 1818-1824.
27. Brodey RS, McGrath JT, Reynolds H. A clinical and radiological study of canine bone neoplasms. I. J Am Vet Med Assoc 1959; 134: 53–71.
28. Brodey RS, Sauer RM, Medway W. Canine Bone Neoplasms. J Am Vet Med Assoc 1963; 143: 471-495.
29. Brodey RS, Riser WH. Canine osteosarcoma. A clinicopathologic study of 194 cases. Clin Orthop Relat Res 1969; 62: 54–64.
30. Dorfman SK, Hurvitz AI, Patnaik AK. Primary and secondary bone tumours in the dog. J Small Anim Pract 1977; 18: 313-326.
31. Breslow N, Day N. Rates and Rate Standardization In: Heseltine E, editor. Statistical Methods in Cancer Research, Vol II. The Design and Analysis of Cohort Studies. International Agency for Research on Cancer, World Health Organization: Lyon, France 1987; 48–79.
32. Wei L, Lin D, Weissfield L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989; 84: 1065–1073.
33. Egenvall A, Nødtvedt A, von Euler H. Bone tumors in a population of 400,000 insured Swedish dogs up to 10 y of age: incidence and survival. Can J Vet Res 2007; 71: 292–299.
34. Stauffer KD, Tuttle TA, Elkins AD, et al. Complications associated with 696 tibial plateau leveling osteotomies (2001–2003). J Am Anim Hosp Assoc 2006; 42: 44–50.
35. Gatineau M, Dupuis J, Plante J, et al. Retrospective study of 476 tibial plateau levelling osteotomy procedures. Rate of subsequent 'pivot shift', meniscal tear and other complications. Vet Comp Orthop Traumatol 2011; 24: 333–341.