

# Solitary osseous plasmacytomas in dogs: 13 cases (2004–2019)

A. J. REISING , L. L. DONNELLY <sup>1</sup>, B. K. FLESNER, C. A. MAITZ AND J. N. BRYAN

Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, Missouri, USA

<sup>1</sup>Corresponding author email: donnellyl@missouri.edu

**OBJECTIVES:** To further characterise solitary osseous plasmacytoma in dogs, an extremely rare disease. To describe diagnosis, disease progression and treatment outcomes in dogs with solitary osseous plasmacytoma.

**MATERIALS AND METHODS:** Retrospective review of dogs with solitary osseous plasmacytomas that were diagnosed and treated at a single institution from 2005 to 2019. Kaplan–Meier single group survival analysis was used to estimate median survival time and progression-free interval.

**RESULTS:** Thirteen dogs met the inclusion criteria for the study, and of those, 11 were treated. The median age at diagnosis was 8 years (range 4 to 11). Most solitary osseous plasmacytomas occurred in the vertebrae (n=8). Other sites included the maxilla (n=2), the mandible (n=1), the tibia (n=1) and the carpus (n=1). The median survival time for all dogs with solitary osseous plasmacytoma was 912 days (range 5 to 2179), and the progression-free interval for treated dogs was 310 days (range 22 to 2179). Most dogs were treated with radiation therapy (n=10) with nine of 10 receiving a definitive, daily fractionated protocol and with five of ten having had neoadjuvant surgery. Seven dogs received chemotherapy, which was initiated after progressive disease in five dogs. The median survival time for dogs that completed radiation therapy (n=9) was 1166 days (range 545 to 2179). While five dogs developed lesions at other sites, no dogs progressed to multiple myeloma.

**CLINICAL SIGNIFICANCE:** Canine solitary osseous plasmacytomas can be managed long term with appropriate local therapy. This observation reflects the biologic behaviour observed in humans.

*Journal of Small Animal Practice* (2021) **62**, 1114–1121  
DOI: 10.1111/jsap.13411

Accepted: 27 July 2021; Published online: 31 August 2021

## INTRODUCTION

Myeloma-related disorders (MRDs) are characterised as clonal plasma cell neoplasms including multiple myeloma (MM), macroglobulinemia, extramedullary plasmacytoma (EMP), solitary osseous plasmacytoma (SOP) and plasma cell leukaemia. MRDs account for approximately 8% of all haematopoietic malignancies and 3.6% of all bone tumours in dogs (Liu *et al.* 1977, Matus *et al.* 1986). There are two localised forms of plasma cell neoplasms described in veterinary medicine: EMPs and SOPs. SOPs are a rare subset of plasmacytic tumours found in the vertebrae, long bones, zygomatic arch or ribs of dogs (MacEwen *et al.* 1984, Matus *et al.* 1986, Rusbridge *et al.* 1999, Vail *et al.* 2020). In humans, these plasma cell tumours of bone are more commonly referred to as solitary bone plasmacytomas (SBPs) and occur most

commonly in the vertebrae, femur and pelvis, though mandibular and maxillary forms have been described (Anil 2007, Kucukkurt *et al.* 2016). It is a rare disease in humans, and men are diagnosed twice as frequently as women (Pham & Mahindra 2019). The standard of care treatment for SBPs in humans is external beam radiation therapy (Kilciksiz *et al.* 2012). Local control rates are greater than 80% for SBPs, and chemotherapy is not used before progression to MM as there is no known benefit (Shih *et al.* 1995, Hu & Yahalom 2000, Dimopoulos & Hamilos 2002, Ozsahin *et al.* 2006, Kilciksiz *et al.* 2008, Kilciksiz *et al.* 2012). Up to 50% of SBPs are reported to progress to MM within 10 years of diagnosis (Kilciksiz *et al.* 2012, Caers *et al.* 2018).

Due to the low incidence of SOPs in dogs, there is very little literature to guide treatment decisions. It has been assumed in the past that the majority of SOPs will progress to MM, but a paucity

of literature describes this phenomenon (MacEwen *et al.* 1984, Rusbridge *et al.* 1999, Vail *et al.* 2020). Diagnosing EMPs or SOPs in dogs requires a tissue sample demonstrating plasma cell neoplasia and diagnostic testing to rule out MM. Ideal full staging to rule out MM would entail complete blood work, urinalysis, assessment for Bence-Jones proteinuria, chest and abdominal imaging to rule out multifocal bone lesions or soft tissue masses, bone marrow examination and serum protein electrophoresis. There is no standard protocol for diagnosing, staging or treating SOP in dogs. The aim of our study is to characterise SOP in dogs and describe treatment protocols and outcomes.

## MATERIALS AND METHODS

An initial medical record query was completed for dogs evaluated between 2004 and 2019. Diagnosis key words used included “plasmacytoma,” “plasma cell tumour,” “multiple myeloma,” “plasma cell tumour-vertebrae,” and “tumour, plasma cell.” Dogs were included in the study if they had a cytologic or histologic diagnosis of a plasma cell neoplasm that originated from bone on imaging. Routine blood work and imaging of the tumour were required minimum staging. Dogs were excluded if they had evidence of MM at the time of diagnosis (multifocal bone lesions, hyperglobulinemia, monoclonal gammopathy), the tumour did not appear to originate from bone, or the tumour type was not confirmed with cytology or histopathology. We used updated MM diagnosis criteria described by Rajkumar *et al.* to define our patient population, but a bone marrow exam was not a required staging test (Rajkumar *et al.* 2014).

For each dog, medical records were reviewed, and the following information was recorded: signalment, weight, presenting complaint, duration of clinical signs before referral, treatment before referral, tumour location, tumour size, cytology and/or histopathology results, immunohistochemistry results, baseline blood work abnormalities, urinalysis abnormalities, urine specific gravity, urine protein to creatinine (UPC) ratio, baseline imaging findings, serum globulin, serum electrophoresis results, presence of hypercalcemia, bone marrow findings, treatment pursued and protocol used, response to treatment including toxicity, date of progressive disease, date of discontinuing therapy and date of death. Pertinent radiation treatment data including fractionation scheme, computer *versus* manual plan, total dose, dose per fraction, number of fractions and whether radiation was delayed or discontinued were recorded. Radiation therapy was defined as definitive or palliative based on fraction size and whether the intent was curative or palliative. Specifically, a dose per fraction equal to or less than 300 cGy was considered a definitive protocol.

Owners were contacted to complete data collection as needed. Veterinary Cooperative Oncology Group (VCOG) (Veterinary Cooperative Oncology Group 2016) and Veterinary Radiation Therapy Oncology Group (VROG) (Ladue & Klein 2001) criteria were used to assess treatment response and toxicity. Side effects that occurred less than 90 days after completion of radiation therapy were considered acute, and a late side effect was defined as any side effect that occurred at least 90 days after completion of

radiation therapy. Objective outcome measures evaluated included progression-free interval (PFI) and median survival time (MST). PFI was calculated from the date of diagnosis to progressive disease in days. In cases where progression was not documented, individuals were censored at the time of their last follow up. Overall survival (OS) was calculated from the date of diagnosis to the date of death in days. Kaplan–Meier single-group survival analysis was generated using SigmaPlot 14 (Systat Software Inc, San Jose CA) to estimate the median survival time (MST).

Radiation plans varied slightly based on location of disease and clinician, but all treatment plans were computer-based (XiO, CMS, St. Louis, MO or RayStation, Raysearch Laboratories, Stockholm, Sweden). All treatment plans were based on pre- and post-contrast CT and dogs were positioned in a vac-lock cradle (SecureVac Immobilisation System, Bionix, Toledo, OH). Relevant organs at risk were contoured, clinical target volume expansions were based on the clinical opinion of the radiation oncologist and planning target volume expansions were based on anatomic location and degree of immobilisation. Computer-based plans were either 3D conformal plans, or step-and-shoot intensity-modulated radiation therapy (IMRT). All linear accelerators and IMRT-based treatment plans were in accordance with a quality assurance programme overseen by a medical physicist. Dogs were treated with either 8MV photons from a Siemens Mevatron (Siemens Healthineers, Erlingen, Germany) or 6MV or 15MV photons delivered by either a Siemens Oncor Impression (Siemens Healthineer, Erlingen, Germany) or a Varian 21EX (Varian Medical Systems, Palo Alto, CA). Accurate positioning was confirmed with daily orthogonal megavoltage portal imaging.

The recommended recheck schedule for all radiation patients was a physical exam 2 weeks, 6 weeks and 3 months following completion of radiation therapy. Recheck CT scans were recommended every 6 months. Assessment of VROG score by tissue type was completed by a boarded radiation oncologist at each recheck (Ladue & Klein 2001).

## RESULTS

### Demographics

Four hundred and sixty dogs were diagnosed with a plasma cell neoplasm from 2004 to 2019. Thirteen dogs met all inclusion criteria for this study. The median age at presentation was 8 years (range 4 to 11). The dogs were mostly castrated males (n=8, 61.5%). The breeds presenting with a SOP were: three mixed breed dogs, one Pomeranian, one Yorkshire terrier, one golden retriever, one Maltese, one Shetland sheepdog, one Miniature Pinscher, one Airedale Terrier, one Labrador retriever, one boxer, and one shih-tzu. Four (30.8%) dogs were classified as large breed (>30 kg), and the median weight was 13.5 kg (range 3.5 to 42.4). Demographic data are summarised in Table 1.

### Location and clinical signs

The majority of tumours were located in vertebrae (n=8, 61.5%). Other sites included the maxilla (n=2), the mandible (n=1), the tibia (n=1) and carpal bones (n=1). Tumour location by dog is

**Table 1. Summary of signalment, diagnostics, presenting signs, and treatment in 13 dogs with solitary osseous plasmacytomas**

Variable	Number of dogs	Median (range)
Age (years)	13	8 (4 to 11)
Sex		
Female	0	
Female spayed	5	
Male	0	
Male neutered	8	
Weight (kg)	13	13.5 (3.5 to 42.4)
Diagnostics		
CT scan or MRI	13	
Chest radiographs	7	
Abdominal ultrasound	3	
Normal	3	
Abnormal	0	
Serum electrophoresis	5	
Monoclonal	0	
Polyclonal	5	
Bone marrow	1	
Signs on presentation		
Neuro signs		
Yes	5	
No	8	
Pain		
Yes	8	
No	5	
Treatment	11	
Surgery		
Yes	6	
No	7	
Radiation		
Yes	10	
No	3	
Chemotherapy		
Yes	7	
No	6	

summarised in Table 2. The most common presenting clinical signs for dogs with vertebral disease were pain (6/8, 75%) and ataxia or paresis (4/8, 50%). The dogs with appendicular tumours also presented with pain. Two of three dogs with jaw tumours presented with bleeding from the mouth. Presenting signs are summarised in Table 1. The median duration of signs before referral was 23 days (range 1 to 70). Other frequent clinical signs included lethargy, diarrhoea, and swelling noted in the area of the tumour.

### Diagnostics

All dogs in this study were evaluated with routine complete blood count (CBC) and serum chemistry. The only documented CBC abnormality was a mild normocytic, normochromic non-regenerative anaemia in two dogs (PCV of 34% and 36%, respectively). The most common serum chemistry abnormality was an increased ALP (n=4, 30.8%). The median reported serum globulin was 3.3 g/dL (range 3.0 to 3.9). One dog had mild hyperglobulinemia measuring 3.9 g/dL (range 2.2 to 3.6) on presentation, and serum protein electrophoresis revealed a polyclonal gammopathy. Four additional dogs with globulin concentrations in the normal reference range had a serum electrophoresis performed, and all were considered polyclonal. No dog had a documented total hypercalcemia. Four dogs had docu-

mented proteinuria on presentation (30.8%), and two of these had a UPC ratio performed. Of these two, one was abnormal (6.5; Dog 7, Table 2). A urine protein electrophoresis was performed but was polyclonal, and a bone marrow aspirate revealed no cytologic abnormalities.

Seven (53.8%) SOPs were diagnosed using histopathology, four (30.8%) were diagnosed using cytology and two (15.4%) utilised both methods. Of those that were diagnosed by histopathology, 66.7% (6/9) used immunohistochemical (IHC) stains to aid in diagnosis. Of the six tumours where IHC was utilised, three stained positive for MUM1, one stained positive for CD79a, one had sparse positive cells for CD3 and one stained positive for lambda light chain. Three samples were stained with lambda light chain, but two were negative. Two samples were stained with CD79a, but one was negative. One third of the tumours diagnosed by histopathology were considered plasma cell based on morphology alone. These results are detailed in Table 3.

All dogs evaluated had solitary lytic bone lesions and were assessed with advanced imaging (CT n=11; MRI n=2). One dog (Dog 1, Table 2) was also evaluated by a nuclear medicine bone scan, which revealed no activity in the area of the tumour; this was unsurprising due to the lytic nature of the tumour. Seven (53.8%) dogs had thoracic radiographs completed and 3 (23.1%) dogs had an abdominal ultrasound. All studies were unremarkable except one dog (Dog 3, Table 3) had a pathologic fracture of C7.

### Treatment

Eleven of 13 dogs were treated for SOP. Of the 11 treated dogs, four dogs were treated with radiation therapy and chemotherapy; three dogs with surgery, radiation therapy and chemotherapy; two dogs with surgery and radiation therapy; one dog with surgery only and one dog with radiation therapy only. No dogs received chemotherapy only. Two dogs were euthanased without therapy. Treatment by individual dog is outlined in Table 2.

The most commonly prescribed treatment was external beam radiation therapy (n=10, 90.9%) with all but one dog receiving a definitive protocol. Dogs 1, 5, 7, 8, 9, 10, 11, 12 and 13 received definitive radiation therapy and Dog 6 received a palliative protocol. Dog 9 was euthanased for pain before completing treatment. Five dogs had surgery before starting radiation (Dogs 1, 8, 9, 10 and 13). For definitive radiation, the median total dose delivered to cover 95% of the planning target volume was 53 Gy (range 48 to 54), and the median number of treatment beams used was 3.5 (range 2 to 6). For three dogs, this information was no longer available. All dogs receiving definitive radiation received fraction sizes no greater than 3 Gy per fraction. The median number of fractions per protocol was 20 (range 14 to 24) for the dogs treated definitively. Dog 6 with a vertebral SOP at C6 received palliative radiation. Two 6 Gy fractions were given 9 days apart and this dog survived 1898 days. All dogs with appendicular and jaw SOPs completed definitive radiation (n=5). Five dogs with vertebral SOP started radiation, and four completed treatment.

Dogs were recommended to be assessed for radiation-associated side effects and response 2 weeks, 6 weeks, 3 months and

**Table 2. Individual dog tumour locations, primary treatment, rescue treatment, location of progression, progression-free interval (PFI), overall survival time (OST) and cause of death**

Dog	SOP location	Primary treatment	Rescue treatment	Location of progression	PFI	OST	Cause of death
1	Vertebra L6	Dorsal laminectomy, definitive RT, melphalan with prednisone	None	N/A	287	1166	Lost to follow-up
2	Vertebra L1	None	N/A	N/A	N/A	5	Quality of life declined: Tumour related
3	Vertebra C7	Fracture stabilisation and decompression of spinal cord	None	N/A	N/A	42	Unknown: collapse and sudden death
4	Vertebra C2	None	N/A	N/A	N/A	5	Cardiac/respiratory arrest
5	Left proximal tibia	Definitive RT	Toceranib phosphate	N/A	None	545	Histiocytic sarcoma
6	Vertebra C6	Palliative RT, vincristine, melphalan and prednisone	Melphalan CTX doxorubicin	Fifth rib	820	1898	Congestive heart failure and visceral hemangiosarcoma
7	Left second and third carpal bones	Definitive RT	CTX melphalan and prednisone vincristine chlorambucil	Skin +/- lung	198	798	Disseminated plasma cell disease; vomiting and diarrhoea
8	Mandible	Rostral mandibulectomy, definitive RT	None	N/A	None	2179	Alive
9	Vertebra T7	Hemilaminectomy and biopsy, definitive RT (did not complete)	None	T7 (primary site)	22	32	Pain: Tumour related
10	Vertebra L2	Hemilaminectomy and biopsy, definitive RT	Melphalan lomustine	T1, third sternebra	310	912	Pain: Tumour related
11	Vertebra T10	Definitive RT	Melphalan COP protocol	L5	293	1358	Tumour related
12	Maxilla	Definitive RT	None	N/A	None	1813	Alive
13	Maxilla	Incisional biopsy with marginal maxillectomy, definitive RT	Melphalan CTX chlorambucil vincristine	Orbit, skin	331	965	Disseminated plasma cell disease and pulmonary nodules: tumour related

COP Cyclophosphamide, vincristine, prednisone chemotherapy, CTX Cyclophosphamide, RT Radiation therapy, SOP Solitary osseous plasmacytoma

**Table 3. Descriptive information regarding tumour location and method of diagnosis for each solitary osseous plasmacytoma**

Patient	SOP location	Diagnostic modality	IHC staining
1	Vertebra L6	Histopathology	Immunoglobulin light chain unable to complete; decalcified tissue too small
2	Vertebra L1	Histopathology	CD79+ and immunoglobulin light chain+
3	Vertebra C7	Both	CD79-, lambda light chain, sparse CD3 + <sup>a</sup>
4	Vertebra C2	Cytology	N/A
5	Tibia	Cytology	N/A
6	Vertebra C6	Cytology	N/A
7	Carpal bones	Both	MUM1+
8	Mandible	Histopathology	No
9	Vertebra T7	Histopathology	MUM1+
10	Vertebra L2	Histopathology	No
11	Vertebra T10	Cytology	N/A
12	Maxilla	Histopathology	MUM1+
13	Maxilla	Histopathology	No

<sup>a</sup>Three cells had faint CD3+ staining, histologic interpretation was round cell tumour; cytology was consistent with plasma cell neoplasm

every 6 months after completing radiation. Of nine dogs that completed radiation, five were evaluated 2 weeks post-radiation for acute side effects, but seven dogs were regularly rechecked by the radiation oncology team. Two dogs rechecked with their

referring veterinarian only. All documented acute and chronic normal tissue effects related to radiation therapy were associated with the skin or the mucous membranes, and acute effects were more common. Six of nine dogs that completed radiation had acute side effects: two Grade 1, two Grade 2, and two Grade 3 noted at their peak. Grade 3 acute radiation tissue side effects were documented in two dogs with jaw tumours and described as painful moist cutaneous desquamation in Dogs 8 and 13. A total of three cases had late side effects (all Grade 1 of the skin). Two dogs (20% of those that received RT) experienced both acute and late effects. In 30%, no normal tissue effects related to radiation were noted. Dog 7 had a pathologic compression fracture of carpal bones shortly after completing definitive radiation therapy and remained mildly lame until death 798 days after diagnosis.

Seven dogs (63.6% of treated dogs) received chemotherapy as part of management of SOP (Table 2). Two received radiation and chemotherapy concurrently, and five started chemotherapy after disease progression. For the five dogs that had chemotherapy after disease progression, the median time to initiation of chemotherapy after starting radiation was 292 days (range 129 to 516). The most commonly prescribed chemotherapeutic was melphalan (n=6, dosage range=0.05 to 0.1 mg/kg PO daily). Other drugs prescribed included vincristine (n=3, dosage range=0.5 to 0.7 mg/m<sup>2</sup> IV once weekly), cyclophosphamide (n=4, dosage=250 mg/m<sup>2</sup> PO over 3 to 4 days), lomustine (n=1, dosage=50

to 70 mg/m<sup>2</sup> PO once q 3 weeks), doxorubicin (n=1, dosage for dogs <15 kg=1 mg/kg IV once q 3 weeks), chlorambucil (n=2, dosage=4 mg/m<sup>2</sup> PO daily) and toceranib phosphate (n=1, dosage=2.55 mg/kg PO EOD). The majority of these agents were utilised once melphalan therapy failed. Solid tumour response criteria were not strictly followed. The most common side effect following melphalan therapy was thrombocytopenia (n=3 dogs, two Grade 1 and one Grade 3). The most common side effect following other chemotherapeutic therapy was neutropenia (n=2 dogs) and was found after administration of cyclophosphamide or vincristine. Grade 1 diarrhoea was noted after toceranib phosphate and chlorambucil administration (given in separate protocols). One dog experienced sterile hemorrhagic cystitis after one dose of cyclophosphamide which was subsequently discontinued. Follow-up was recommended based on drug protocol and attending clinician preference.

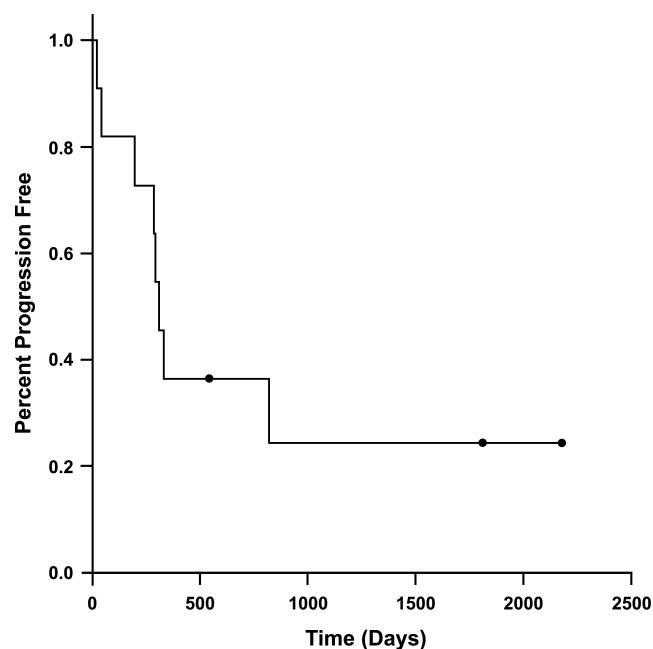
### Response to therapy

Response to therapy was assessed based on clinical signs and radiologic exams. Five of 11 treated dogs were evaluated for disease response with CT, and three were evaluated with radiography only. Radiologic lesion improvement was documented in six of eight evaluable dogs (Dogs 1, 5, 6, 7, 10 and 13). Dogs 1 and 6 were receiving chemotherapy at the time of documented clinical improvement and radiologic response, but both had also received radiation. The four other dogs (Dogs 5, 7, 10 and 13) with radiographically documented tumour response had not received chemotherapy. After starting rescue chemotherapy, imaging was performed less frequently, but no radiologic responses were noted in this setting. Two treated dogs had no recheck imaging (Dogs 8 and 12) and were alive at the time of manuscript preparation with no visible recurrence of oral lesion more than 1800 days post-treatment. Radiologic responses were often delayed compared to clinical responses with a median time to clinical response of 30 days (range 1 to 83) and a median time to radiologic response (defined as subjectively reduced lysis and new bone production around the lesion) of 123 days (range 82 to 196). Recheck intervals and imaging modality varied. Hundred percent of treated dogs (n=11) improved clinically with eight (72.7%) of 11 dogs experiencing complete resolution of clinical signs.

Of the 13 dogs in this study, four died within 45 days of diagnosis, and all had vertebral tumours. Two dogs (Dog 2 and 4) were euthanased or died within a week of presentation and were not treated. Dog 9 improved clinically following hemilaminectomy of T7 but was euthanased for pain 32 days after diagnosis without completing radiation. Dog 3 originally presented paraplegic and had surgery to stabilise a pathologic fracture of C7. Dog 3 was neurologically normal 1 month after surgery but died 42 days after surgery without known cause; post-mortem examination was not performed.

### Progression and survival

Individual dog progression and survival is outlined in Table 2. Ten dogs were evaluated for disease progression, and four (40%) of these never progressed. The median PFI for 11 treated dogs was 310 days (range 22 to 2179 days) (Fig. 1). Two dogs (Dog



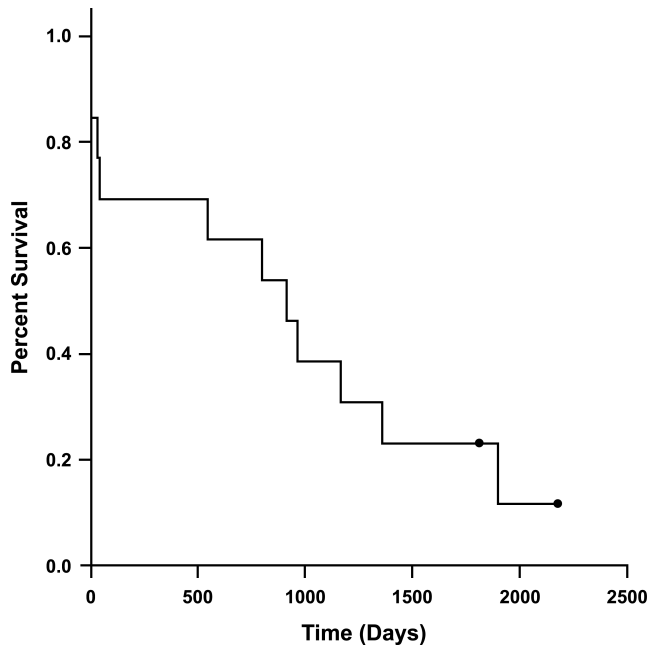
**FIG 1.** Kaplan–Meier curve estimating the progression-free interval (PFI) (median PFI 310 days; range 22 to 2179 days) of 11 dogs treated for solitary osseous plasmacytoma. Black dots indicate censored observations which were dogs with no noted disease progression

8 and 12) never progressed that were alive and disease free at 1813 days and 2179 days from diagnosis, both with jaw SOP location treated with definitive radiation therapy. Two dogs died without SOP progression, one (Dog 5) from metastatic histiocytic sarcoma (CD3-, CD18+, Iba1+, Mum1-) 545 days after diagnosis and the other (Dog 1) with no cause of death recorded 1166 days after diagnosis. Of the six dogs with documented disease progression, three developed new bone lesions (1 rib; 1 sternbra and T1 vertebral body; and 1 L5 vertebral body). One of the dogs with documented progression (Dog 7) developed simultaneous skin and lung lesions; lung nodules were not aspirated, but skin nodules were confirmed plasma cell neoplasia by cytology. Dog 13 was treated with surgery and definitive radiation for a left rostral maxillary SOP developed an EMP in the left orbit that surrounded the optic nerve 331 days after diagnosis. Cytology confirmed the orbital mass to be plasma cell neoplasia; treatment with definitive radiation to the orbital lesion resulted in a CR and a second PFI of 467 days. At the time of second progression and similar to Dog 7, Dog 13 developed plasmacytomas in the skin and a lung nodule verified by CT scan but not cytology. The final dog with documented progression (Dog 9) experienced uncontrolled pain that was recorded as local disease progression 22 days after diagnosis. No cases developed total hypercalcemia at the time of progression, and of the two cases with recheck serum electrophoresis for mild hyperglobulinemia, both were polyclonal.

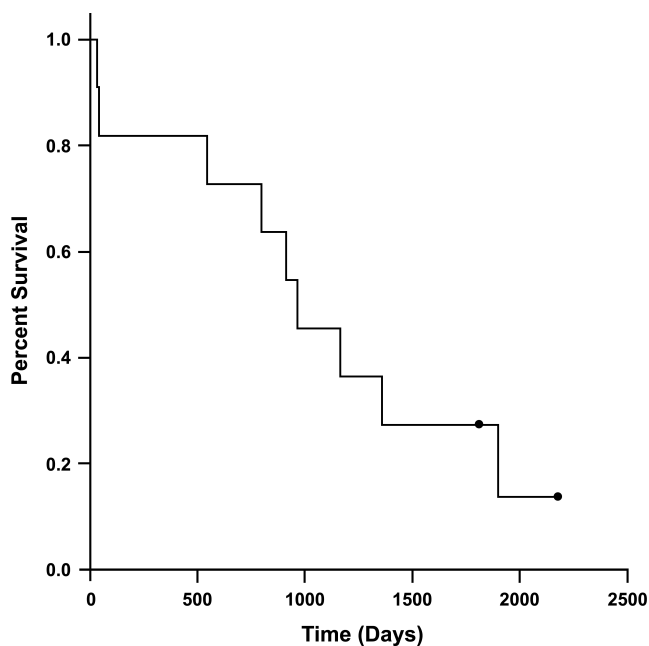
Two dogs (Dog 8 and 12) were alive at the time of manuscript preparation and were censored at the time of their last follow-up. Of those that died (n=11), six (2, 7, 9, 10, 11 and 13) definitively died of plasma cell neoplasia (54.5%). The MST of all 13 dogs diagnosed with SOP was 912 days (range 5 to 2179) (Fig. 2). The

MST for the 11 dogs treated for SOP was 965 days (range 32 to 2179 days) (Fig. 3).

The impact of treatment modality on survival is unknown, but of 10 dogs that received radiation therapy, five also had surgery (three laminectomies, one rostral mandibulectomy and one marginal maxillectomy). The MST for those that had surgery



**FIG 2.** Kaplan–Meier curve estimating the overall survival [median survival time (MST) 912 days; range 5 to 2179] of 13 dogs diagnosed with solitary osseous plasmacytoma. Black dots indicate censored observations which were dogs alive at the time of manuscript preparation



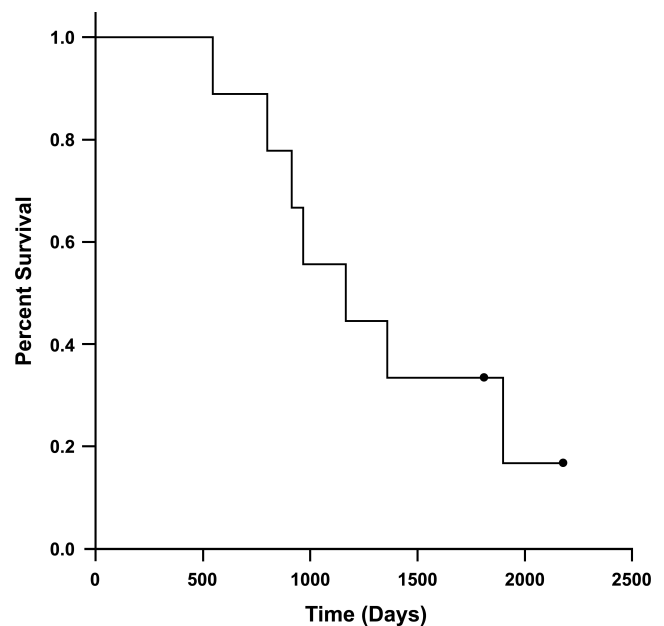
**FIG 3.** Kaplan–Meier curve estimating the survival [median survival time (MST) 965 days; range 32 to 2179] of 11 dogs treated for solitary osseous plasmacytoma. Black dots indicate censored observations which were dogs alive at the time of manuscript preparation

and radiation was 912 days (range 32 to 2179). For the nine dogs that completed planned radiation therapy, the median survival time was 1166 days (range 545 to 2179) (Fig. 4). Two of these dogs were still alive at the time of manuscript preparation (Dogs 8 and 12). Of these two dogs, the locations of their tumours were the mandible and maxilla. Dog 6 received hypofractionated radiation therapy and lived 1898 days. The MST for dogs with vertebral SOP regardless of therapy (n=8, 61.5%) was 42 days (range 5 to 1898 days). The MST for dogs with non-vertebral SOP (jaw or appendicular) (n=5, 38.5%) was 965 days (range 545 to 2179 days).

## DISCUSSION

Limited information exists to guide diagnostic and treatment decisions for dogs with SOPs, and this is the first case series dedicated specifically to this disease entity. This is, in part, due to the rare incidence of this disease and probable frequent euthanasia before diagnosis due to severity of clinical signs associated with this tumour type. Only 2% of dogs diagnosed with plasma cell malignancies at our institution met inclusion criteria for this study. Our goal was to describe presentation and outcome of a series of dogs with confirmed SOPs from a single institution.

Most dogs in this study presented with pain and/or neurologic deficits with vertebral location being most common. External beam radiation therapy was the primary therapy for 10 of 13 dogs, and five of 10 underwent neoadjuvant surgery for spinal decompression or diagnosis. Historically, treatment of SOPs in dogs has aimed to control local disease with the use of surgery and radiation therapy. Radiation therapy is the standard of care



**FIG 4.** Kaplan–Meier curve estimating the survival [median survival time (MST) 1166 days; range 545 to 2179] of nine dogs diagnosed with solitary osseous plasmacytoma that completed radiation therapy. Black dots indicate censored observations which were dogs alive at the time of manuscript preparation

in human medicine with a total fractionated dose of 40 to 50 Gy given over 4 weeks (1.8 to 2.0 Gy per fraction) and 2 cm clinical target expansion is considered optimal (Caers *et al.* 2018, Tsang *et al.* 2018). Unfortunately, information regarding the clinical target expansion was not available for most of the dogs in this series, but in general, our group aims for 0.5 to 2.0 cm depending on tumour location. Whether surgery before radiation resulted in improved tumour control is unknown and may have added morbidity and certainly cost.

Based on 100% clinical improvement and a MST of 965 days (range 32 to 2179 days) for treated dogs in this study, the prognosis for SOP is good with aggressive local therapy, but it has often been stated that the majority of SOP cases in dogs will progress to MM (MacEwen *et al.* 1984, Rusbridge *et al.* 1999, Vail *et al.* 2020). The rate and timeframe for systemic spread is not well characterised, and when to institute systemic therapy is a dilemma. In people, 50% of SBP cases progress to MM within 10 years (Kilciksiz *et al.* 2012, Caers *et al.* 2018). While new lesions were noted in five dogs, no case in this series met described criteria for MM (Rajkumar *et al.* 2014). However, a major limitation to our study is its retrospective nature and lack of standardised re-staging, including bone marrow evaluations, which could have falsely inflated our response duration and lack of MM discovery. In humans, bone marrow aspirates and biopsies are a mainstay of the initial workup for a suspected SBP and are necessary for adequate follow-up to detect any evidence of systemic progression (Kilciksiz *et al.* 2012, Caers *et al.* 2018). It has been documented that human patients with minimal bone marrow plasmacytosis at the time of diagnosis have an increased risk of progression to MM over time (Kilciksiz *et al.* 2012, Caers *et al.* 2018). This phenomenon has yet to be documented in dogs and may be a vital component of adequate staging for affected dogs in the future.

Systemic therapy for SBP is not pursued in humans until MRD or MM develops, which could be months or often years later (Kilciksiz *et al.* 2012, Caers *et al.* 2018). Studies in human medicine have found no benefit to starting chemotherapy before systemic disease is documented (Rusbridge *et al.* 1999). Local control was the primary aim for the dogs in this study as the utility of chemotherapy in dogs with SOP remains questionable. In the present study, seven dogs received chemotherapy as part of the treatment regimen with five starting after progression of disease, similar to the human approach. Two dogs (Dogs 1 and 6) received chemotherapy simultaneously with radiation, which deviates from human protocols. Due to a lack of evidence for treatment recommendations for SOP in dogs, chemotherapy strategies differed by clinician in this retrospective study.

In this case series, five of six dogs with documented disease progression developed new plasma cell tumours at distant sites. None were receiving chemotherapy at the time of progression. Whether early use of chemotherapy could have delayed new tumour development is unknown. After disease progression, chemotherapy was started and may have prevented detection of progression to MM. A recent multi-institutional retrospective study by Elliott *et al.* reported four dogs with SOP that were treated with radiation therapy and chemotherapy (Elliott *et al.* 2020). All dogs received melphalan and prednisone either immediately

before or after radiation therapy. Two dogs were deemed to have progression of their plasmacytic disease; true progression to MM, though, was not confirmed. Prospective studies are needed to assess the potential benefit of systemic therapy for SOP in dogs.

Cytology was used to diagnose four of 13 cases of SOP in this series. Histopathology with IHC stains remains gold standard for definitive diagnosis of plasma cell tumours. Specifically, use of stains such as MUM1, lambda light chain and CD79a can be used to further validate a diagnosis of plasma cell tumour. When a biopsy cannot be obtained, immunocytochemistry (ICC) could be considered, but ICC was not used in this case series.

In regards to dog signalment, the majority of our cases were male (61.5%). An overrepresentation of males has been documented in humans with this disease by at least 2:1, and this has been previously noted in dogs with plasma cell neoplasia (Rusbridge *et al.* 1999, Nahi *et al.* 2017). Indeed, males were over-represented in the Elliott cases series: 22 out of 30 dogs with macroscopic plasma cell tumours were neutered males (Elliott *et al.* 2020). In contrast to the most common primary bone tumour in dogs, osteosarcoma, where large and giant breeds are far over-represented, the median weight for our cohort of dogs was 13.5 kg (range 3.5 to 42.4) (Withrow *et al.* 1991). Small breeds dominated in our study.

MST and PFI were prolonged (912 and 310 days, respectively) in dogs with SOP. Of note, dogs with jaw SOP, two originating in the maxilla and one in the mandible, did exceptionally well. This may be attributed to a difference in tumour behaviour by location, early detection or even curative intent of treatment in these cases. Various combinations of therapies were noted in the 11 treated dogs with radiation and chemotherapy being the most common combination. Based on the dogs in this series, it appears that definitive radiation therapy is effective for long-term control. Systemic therapy may confer a benefit if progression to MRD or MM is noted; the benefit of chemotherapy before disease progression is unknown.

Baseline staging tests should attempt to rule out the presence of MM and therefore include baseline serum protein electrophoresis, tumour biopsy with appropriate IHC stains and bone marrow aspirate. Bone marrow aspiration at re-staging could be considered to screen for an early indicator of systemic progression. These tools have proven very useful for monitoring in humans and can help tailor therapy.

Overall, SOP is a rare disease. Survival times and PFIs may be prolonged with combination therapy. In particular, most dogs in this series that received radiation therapy experienced long-term tumour control. Additional studies are needed to assess the optimal use of systemic therapy for dogs with SOP.

### Acknowledgement

The authors would like to thank Teresa Egbert and Justin Cermak.

### Conflict of interest

No conflicts of interest have been declared.

### References

Anil, S. (2007) Solitary plasmacytoma of the maxilla – a case report and review of the literature. *General Dentistry* **55**, 39-43

- Caers, J., Paiva, B., Zamagni, E., et al. (2018) Diagnosis, treatment, and response assessment in solitary plasmacytoma: updated recommendations from a European Expert Panel. *Journal of Hematology and Oncology* **11**, 10
- Dimopoulos, M. A. & Hamilos, G. (2002) Solitary bone plasmacytoma and extramedullary plasmacytoma. *Current Treatment Options in Oncology* **3**, 255-259
- Elliott, J., Looper, J., Keyerleber, M., et al. (2020) Response and outcome following radiation therapy of macroscopic canine plasma cell tumours. *Veterinary and Comparative Oncology* **18**, 718-726
- Hu, K. & Yahalom, J. (2000) Radiotherapy in the management of plasma cell tumors. *Oncology (Williston Park)* **14**, 101-108, 111; discussion 111-102, 115
- Kilciksiz, S., Celik, O. K., Pak, Y., et al. (2008) Clinical and prognostic features of plasmacytomas: a multicenter study of Turkish Oncology Group-Sarcoma Working Party. *American Journal of Hematology* **83**, 702-707
- Kilciksiz, S., Karakoyun-Celik, O., Agaoglu, F. Y., et al. (2012) A review for solitary plasmacytoma of bone and extramedullary plasmacytoma. *ScientificWorld-Journal* **2012**, 895765
- Kucukkurt, S., Karan, N. B., Senguven, B., et al. (2016) Solitary plasmacytoma of the mandible: report of two cases. *BMJ Case Reports* **2016**, bcr2015214255
- Ladue, T. & Klein, M. K. (2001) Toxicity criteria of the veterinary radiation therapy oncology group. *Veterinary Radiology and Ultrasound* **42**, 475-476
- Liu, S. K., Dorfman, H. D., Hurvitz, A. I., et al. (1977) Primary and secondary bone tumours in the dog. *Journal of Small Animal Practice* **18**, 313-326
- MacEwen, E. G., Patnaik, A. K., Hurvitz, A. I., et al. (1984) Nonsecretory multiple myeloma in two dogs. *Journal of the American Veterinary Medical Association* **184**, 1283-1286
- Matus, R. E., Leifer, C. E., MacEwen, E. G., et al. (1986) Prognostic factors for multiple myeloma in the dog. *Journal of the American Veterinary Medical Association* **188**, 1288-1292
- Nahi, H., Genell, A., Wälinder, G., et al. (2017) Incidence, characteristics, and outcome of solitary plasmacytoma and plasma cell leukemia. Population-based data from the Swedish Myeloma Register. *European Journal of Haematology* **99**, 216-222
- Ozsahin, M., Tsang, R. W., Poortmans, P., et al. (2006) Outcomes and patterns of failure in solitary plasmacytoma: a multicenter Rare Cancer Network study of 258 patients. *International Journal of Radiation Oncology, Biology, Physics* **64**, 210-217
- Pham, A. & Mahindra, A. (2019) Solitary plasmacytoma: a review of diagnosis and management. *Current Hematologic Malignancy Reports* **14**, 63-69
- Rajkumar, S. V., Dimopoulos, M. A., Palumbo, A., et al. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* **15**, e538-e548
- Rusbridge, C., Wheeler, S. J., Lamb, C. R., et al. (1999) Vertebral plasma cell tumors in 8 dogs. *Journal of Veterinary Internal Medicine* **13**, 126-133
- Shih, L. Y., Dunn, P., Leung, W. M., et al. (1995) Localised plasmacytomas in Taiwan: comparison between extramedullary plasmacytoma and solitary plasmacytoma of bone. *British Journal of Cancer* **71**, 128-133
- Tsang, R. W., Campbell, B. A., Goda, J. S., et al. (2018) Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the International Lymphoma Radiation Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* **101**, 794-808
- Vail, D. M., Thamm, D. H. & Liptak, J. M. (2020) Withrow & MacEwen's Small Animal Clinical Oncology. 6th edn. Elsevier Saunders, St. Louis, MI, USA. p 841
- Veterinary Cooperative Oncology Group (2016) Veterinary cooperative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Veterinary and Comparative Oncology* **14**, 417-446
- Withrow, S. J., Powers, B. E., Straw, R. C., et al. (1991) Comparative aspects of osteosarcoma. Dog versus man. *Clinical Orthopaedics and Related Research* **270**, 159-168