ORIGINAL ARTICLE

Clinical, pathological and prognostic features of surgically excised cutaneous and subcutaneous digital and distal limb mast cell tumours in dogs

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Objective: To evaluate clinical, pathological and prognostic features and outcomes of dogs with surgically excised cutaneous and subcutaneous digital or distal limb mast cell tumours.

Materials and Methods: Medical records between 2014 and 2024 were reviewed, and signalment, clinicopathological testing, tumour location, recurrence, complications and histological characteristics were recorded. Additionally, progression-free interval and overall survival time were evaluated. One hundred and fifteen client-owned dogs with mast cell tumour admitted to two academic institutions were included.

Results: Surgical complications occurred in 38% of dogs with surgical site infection and incisional dehiscence most common. Local recurrence occurred in 23% of dogs overall, with completely excised tumours having 10% recurrence, narrowly excised 20% and incompletely excised 35%. Higher recurrence rates occurred with incomplete surgical margins, mitotic count >5 and histologically high-grade mast cell tumours. The median progression-free interval was significantly longer for wide excision (2270 days) compared to marginal excision (888 days). The overall survival time was 7 years for all dogs overall, was not reached for low-grade mast cell tumours and was 3 years for high-grade mast cell tumours. The progression-free interval and overall survival time were affected by tumour grade but not lymph node status.

Clinical Significance: The behaviour of canine mast cell tumours affecting the digits and distal limb was affected primarily by tumours grade. Recurrence rates were highest in dogs with high-grade mast cell tumours, incomplete surgical resection and a mitotic count of >5. The outcome with surgical excision is excellent. Future studies are needed to further evaluate the effects of adjuvant chemotherapy, metastatic lymph node status and lymph node extirpation in high-grade mast cell tumour cases.

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INTRODUCTION

Mast cell tumours (MCTs) are the most commonly diagnosed canine malignant skin tumours (London & Thamm, 2019). MCT biologic behaviour is variable, and evaluation of prognostic factors is essential to help predict prognosis (Horta et al., 2018). Anatomic location has been shown to be prognostic, with mucous membrane locations such as the prepuce, vulva, nose and oral cavity having a higher risk for metastasis and tumour-related death (Elliott et al., 2016; Khoo et al., 2017; London & Thamm, 2019; Thamm et al., 2006). MCTs affecting the pinna also demonstrate more aggressive biologic behaviour and a higher frequency of lymph node (LN) metastasis in about 50% of cases (Chalfon et al., 2023). Visceral MCTs affecting the spleen, liver or intestines was shown to have the poorest prognosis in a population of small breed dogs, with an average survival of 2 months following diagnosis (Takahashi et al., 2000). MCTs tumours of the perineal and inguinal region behave based on the Kiupel grade and LN status according to the most recent literature (Cahalane et al., 2004; Reynolds et al., 2019; Ribeiro et al., 2022; Sfiligoi et al., 2005). Although several studies have described prognostic indicators for varying locations of MCTs, there remains a paucity of information evaluating the behaviour of canine digital and distal limb MCT.

Historically, a subungual location of MCTs has been associated with aggressive biologic behaviour and a predisposition for LN metastasis (London & Thamm, 2019). However, this information is limited to clinical experience and small numbers of cases within larger retrospective studies (Marino et al., 1995; Wobeser et al., 2007). MCTs affecting the digits is uncommon and accounts for only 6% of digit amputations performed for neoplasia (Wobeser et al., 2007). Digital tumour location has been shown to be prognostic for some types of digital neoplasia such as osteosarcoma, with digital osteosarcoma having a more favourable prognosis compared to other locations (Tremolada et al., 2021). Furthermore, the biologic behaviour of digital masses varies based on tumour type and whether the tumour arises from haired or non-haired skin. For example, digital melanomas on haired skin are more likely to demonstrate less aggressive behaviour compared to melanomas of the footpad being more likely to demonstrate aggressive biologic behaviour compared to cutaneous melanomas (Jeon et al., 2022; Laver et al., 2018). The region of the distal limb and digits can be challenging to perform surgery on, being a site with limited skin for reconstruction. This may lead the surgeon to consider more conservative excision strategies in conjunction with ancillary treatments such as radiation therapy or neoadjuvant chemotherapy to reduce the size of the tumour, possibly increasing the chances of complete removal (Ciammaichella et al., 2024; Ossowska et al., 2023). Investigation of digital and distal limb MCTs is needed to determine prognostic factors and evaluate differences in biologic behaviour for this tumour type in this region.

The purpose of this study was to retrospectively evaluate the clinical, pathological, prognostic features and outcomes of dogs with surgically excised digital or distal limb MCTs. Additionally, the authors aimed to investigate the effects of surgical margins, tumour grade, LN status and treatment with adjuvant chemotherapy on outcome.

MATERIALS AND METHODS

Study design, medical record search, and data collection

A medical record review for dogs undergoing surgical excision of digital or distal limb MCT between 1 January 2014 and 1 March 2024 was performed at two academic veterinary hospitals. Medical records from this time period were searched through each institution's medical record systems (ezyVet, ezyVet, Auckland, New Zealand; StringSoft, StringSoft Inc, Manchester, NH). The species was set to canine and then the keywords of "digital tumour", "toe amputation" and "mast cell tumour" were searched via the medical record system search function. A single investigator searched the medical records for inclusion criteria. Dogs were included if they had a cutaneous or subcutaneous digital or distal limb MCTs (defined as below the carpus or tarsus), the MCT was surgically excised and histological evaluation was completed by a board-certified pathologist describing the grade for cutaneous MCTs based on Kiupel and Patnaik MCT scoring scales (Kiupel et al., 2011; Patnaik et al., 1984) and prognostic histological characteristics for subcutaneous MCT (multinucleation, mitotic count and infiltrative growth pattern), and case follow-up of at least 6 weeks. Included dogs were added to a spreadsheet (Microsoft Excel 365, Microsoft Corporation, Redmond, WA) with one row for each individual consultation. Dogs were excluded if they did not undergo surgery as a first-line treatment, when medical records were incomplete, or if dogs had distant metastasis at the time of evaluation. Data retrieved from medical records included signalment, clinical signs, anatomic location of MCT, tumour dimensions, perioperative staging, surgical dose, margin status, mitotic count, histopathological grade, LN status (Weishaar grading classification HN1 to HN3), adjunctive treatments performed (chemotherapy, radiation therapy and scar revision), local recurrence, systemic metastasis and *de novo* MCT formation (Weishaar et al., 2014). All owners were offered full staging at the time of MCT diagnosis as the recommended gold standard. Clinicians attempted to aspirate the regional lymph node (RLN), superficial cervical LN (prescapular) for forelimb digital and distal limb masses and popliteal LN for hindlimb digital and distal limb masses. The other possible RLN for the forelimb is the axillary LN and for the hindlimb the inguinal LN. Extirpation of these LNs was performed if the LN was metastatic on cytology and if the node was normal on cytology, LN extirpation was based on clinician preference. There were no definitive criteria for LN extirpation in this retrospective study and sentinel lymph node (SLN) mapping was not performed. Surgical dose was decided based on tumour location, size of tumour and owner's goals. If the tumour was digital or interdigital, proportional margins were often feasible through digital or partial foot amputation. If the tumour was located on the metacarpus or metatarsus regional anatomy constraints often only allowed for marginal excision or a more radical surgical dose such as an amputation. All surgical doses and treatment options were discussed with owners along with risks and complications of each procedure. Ultimately, owners elected the surgical dose based on their personal goals for their pet's cancer treatment. A wide surgical approach for MCT resection was based on proportional margins with the tumours <2 cm being resected with margins equal to the width of the tumour and tumours >2 cm being resected with 2 cm margins and a fascial plane deep. Fascial planes were taken as described by Latifi et al. (2022, 2024). When wide surgical approach was not possible, then a marginal excision was performed with 0.5 to 1 cm margins laterally and a deep subcutaneous layer as the deep margin. Surgical margins were assessed via histopathology using the radial margins technique (Kamstock et al., 2011). Complete surgical margins were classified as those with >5 mm or greater of healthy tissue at the lateral margin and a fascial plane deep and narrow surgical margins (clean but close) with 1 to 4 mm of healthy tissue at the lateral and deep margin (Monteiro et al., 2011). Incomplete surgical margins had tumour cells abutting the lateral and/or deep margin. LN histopathology was graded based on the HN1 to HN3 Weishaar grading scale (Weishaar et al., 2014).

Patient follow-up

Intraoperative and postoperative complications were evaluated using the Accordion Severity Classification of Postoperative Complications (Follette et al., 2020). Level 1 complications included mild complications that required only minor procedures or administration of medications. Level 2 complications included moderate complications that required drugs other than those allowed for minor complications (blood transfusions). Level 3 complications included severe complications requiring reoperation or complications resulting in failure of one or more organ systems. Level 4 complications included death.

For long-term follow-up, an active monitoring plan was recommended for dogs with low-grade MCTs to include a physical exam, scar palpation, RLN palpation and evaluation for new masses every 3 months. For high-grade MCTs and dogs with low-grade MCTs with HN3 LNs, the above recommendations were performed in conjunction with an abdominal ultrasound for staging with aspirates of the liver and spleen. MCT scar revision was offered to owners if feasible to attempt to gain clean margins based on regional anatomy. Radiation therapy was offered to owners in the case of Kiupel high-grade MCT with incomplete margins. Chemotherapy was offered to owners with dogs with a Kiupel high-grade MCT or a Kiupel low-grade MCT with HN3 LN. Follow-up was performed through the referral institution or primary veterinarian. Information from follow-up was collected from the referral institution database, record request from the primary veterinarian and owner follow-up by phone.

Statistical analysis

Descriptive statistics were used to report characteristics of dogs with digital and distal limb MCTs. Demographic factors (age, sex and weight), surgical margins, MCT tumour grade, mitotic count, tumour size, metastatic LN status, surgical dose (digit amputation, partial foot amputation, partial limb amputation and full limb amputation) and chemotherapy use were factors evaluated for effect on outcome using log-rank analysis. Oncologic outcomes measured were progression-free interval (PFI) and overall survival time (OST). The PFI and OST were estimated using Kaplan–Meier analysis. PFI was defined as the time from surgery to evidence of local recurrence, metastasis or *de novo* MCT formation. The OST was defined as the time from surgical treatment to death. Dogs that died due to non-MCT-related conditions, were still alive at the time of manuscript preparation, or were lost to follow-up were censored. Chi-square analysis was used to compare proportions. Statistical analyses were performed using statistical software (GraphPad Prism, GraphPad Software).

RESULTS

Population summary, signalment and clinical signs

A single investigator identified 3,300 cases at the two participating academic institutions of canine MCTs treated with surgical excision. One hundred and fifteen dogs met case inclusion (3.5%). The median age at diagnosis was 7 years (range: 1 to 16 years). The median body weight was 28.1 kg (range: 2.4 to 58 kg). The median clinical sign duration was 4 weeks (range: 0 to 104 weeks) with the most common clinical sign being licking the area surrounding and including the tumour. The median tumour size (longest dimension) was 2 cm (range: 0.3 to 7 cm). Case signalment for digital and distal limb MCTs is shown in Table 1.

Pre-treatment diagnostics

Imaging was performed in 9/115 dogs and consisted of radiographs of the manus or pes. No radiograph demonstrated bone lysis adjacent to the digital or distal limb MCTs. Staging was performed at MCT diagnosis in 56/115 dogs, postoperatively in 37/115 cases and not performed in 22/115 cases. All owners were offered full staging at the time of MCT diagnosis as the recommended gold standard. The diagnostics performed are shown in Table 2.

Palpation of the RLN based on anatomic location of the tumour was performed in all dogs. For the forelimb, the superficial cervical and axillary LNs were palpated. For the hindlimb, the popliteal and inguinal LNs were palpated. Normal LN size on palpation was recorded in 72/115 cases, moderate LN

Table 1. Case signalment for dogs with digital and distal limb mast cell tumours

Case signalment for digital and distal limb mast cell tumours	
Sex	
Spayed female	61/115
Intact female	5/115
Neutered male	46/115
Intact male	3/115
Breed	
Mixed breed	45/115
Labrador retriever	15/115
Golden retriever	13/115
Boxer	7/115
Staffordshire terrier	5/115
French bulldog	4/115
Bernese mountain dog	3/115
Pug	3/115
Bulldog	2/115
Maltese	2/115
German shorthaired pointer	2/115
Other purebred (one case each)	14/115

Table 2. Staging for dogs with digital and distal limb cutaneous and subcutaneous mast cell tumours

Staging for digital and distal limb mast cell tumours	
Abdominal ultrasound (AUS)	4/93
Thoracic radiographs	3/93
FNA of locoregional lymph nodes (LN)	14/93
Thoracic radiographs + FNA of LN	4/93
Thoracic radiographs + AUS	9/93
FNA of LN + AUS	12/93
Thoracic radiographs + FNA of LN + AUS	14/93
Thoracic radiographs + FNA of LN + AUS with aspirates of the liver and spleen	6/93
Thoracic radiographs + FNA of LN + AUS with aspirates of the spleen	2/93
FNA of LN + AUS with aspirates of the liver and spleen	10/93
FNA of LN + AUS with aspirates of the spleen	5/93
FNA of LN + AUS with aspirates of the liver	3/93
AUS with aspirates of the spleen	1/93
AUS with aspirates of the liver and spleen	2/93
Thoracic radiographs + AUS with aspirates of the liver and spleen	4/93

Abbreviation: FNA, Fine needle aspiration.

enlargement in 24/115 dogs and marked enlargement in 19/115 dogs. For forelimb digital and distal limb MCTs, there was moderate superficial cervical LN enlargement in 10/56 dogs and marked superficial cervical LN enlargement in 9/56 dogs; no dogs had palpable axillary LN enlargement. For hindlimb digital and distal limb MCTs, there was moderate popliteal LN enlargement in 14/59 dogs and marked popliteal LN enlargement in 10/59 dogs. Fine needle aspiration (FNA) of the RLN was performed in 66/115 dogs. RLNs were attempted to be aspirated whether they were enlarged or not on physical exam. Cytology of the RLN was reactive in 33/66 dogs (50%) and cytologically metastatic in 33/66 LNs (50%).

Tumour location, size and treatments performed

The MCT location was interdigital in 45/115 dogs, digital in 40/115 dogs and on the metacarpus or metatarsus in 30/115 cases. Two dogs had MCT recurrence at the surgical site at the time of tertiary referral following local surgical treatment with their primary veterinarian. No MCTs had a subungual location. The median maximal tumour dimension was 2 cm (range: 0.3 to 7 cm). Cutaneous MCTs accounted for 90% of cases and subcutaneous MCTs for 10% of cases. RLN extirpation was performed in 58/115 dogs based on findings on physical exam, cytological concern for metastasis and clinician preference. The most common surgical approach was marginal excision (47/115), followed by digit amputation (33/115), partial foot amputation (26/115), full limb amputation (8/115) and partial limb amputation (1/115). Digit amputation, partial foot amputation, full limb amputation and partial limb amputation were classified as wide surgical doses (68/115). No dogs received local or axial pattern flaps for resection of MCT in these regions. However, one dog did receive ongoing wound management following dehiscence of a free skin graft on the metatarsus.

Surgical complications occurred in 38% of dogs. Most complications were level I (98%) and were surgical site infection (SSI) and incisional dehiscence. Incisional dehiscence was seen in 35% of cases (41/115) and SSI was seen in 10% of cases (12/115). One case had a level III complication (2%) with severe dehiscence of a free skin graft requiring further surgical intervention and open wound management. Complications occurred in 40% of marginal excisions, 44% of digit amputations, 35% of partial foot amputations, 100% of partial limb amputations and 0% of full limb amputations. Most complications were mild SSI and incisional dehiscence that resolved with oral antibiotics, topical antibiotics and bandaging for 1 to 3 weeks. Only one dog had incisional dehiscence requiring revision surgery.

Histopathology

For cutaneous MCTs, 75% were low grade (76/103) and 25% were high grade (27/103) based on the Patnaik and Kiupel 2-tier grading system. For subcutaneous MCTs, 92% (11/12) demonstrated features associated with less aggressive biologic behaviour with low mitotic count and no evidence of multinucleation or infiltrative growth pattern. Only one subcutaneous MCTs demonstrated histopathological features associated with aggressive biologic behaviour. Mitotic count in histopathology reports was recorded as mitoses/10 high power field (hpf) in 107/115 cases and as mitoses/2.37 mm^2 in 8/115 cases. The median mitotic count was 1 mitosis/10 hpf (range: 0 to 47 mitoses). Surgical margins were complete on histopathology in 38/115 dogs, narrow in 28/115 cases and incomplete in 49/115 cases.

RLN extirpation was performed in 58/115 cases: 52% of low-grade MCTs (40/76) and 55% of high-grade MCTs (15/27). RLN extirpation consisted of 24 superficial cervical (prescapular) LN and 34 popliteal LN. LN extirpation was performed in 25% of subcutaneous MCTs (3/12). Cytology and histopathological evaluation of the same LN were available in 60% of cases (40/66). Cytology for diagnosis of a metastatic *versus* non-metastatic LN agreed with histopathology in 85% of cases (34/40). LN metastasis was most common in high-grade MCTs at 45% (12/27), followed by low-grade MCTs at 27% (21/76) and least common with subcutaneous MCTs at 8% (1/12). The breakdown of LN HN grade for cutaneous and subcutaneous MCTs is shown in Table 3.

Metastatic disease was diagnosed at the time of surgery in 34/115 cases based on LN pathology. Two dogs having low-grade MCTs received chemotherapy (vinblastine+prednisolone) due to the presence of an HN3 LN. Following surgical treatment, an additional 24 dogs were diagnosed with metastatic disease at follow-up staging visits. The median time to metastatic disease detection was 628 days (range: 11 to 2724 days). Most dogs had metastatic disease detected in the RLN (16/24). The minority of dogs had metastatic disease diagnosed in a distant LN (3/24) or visceral metastasis in the liver and spleen (5/24). For dogs diagnosed with metastatic disease at follow-up visits, 50% (12/24) clients elected additional treatment, and 50% (12/24) elected palliative care. Metastatic LN extirpation was performed as the sole adjuvant treatment in 2/12 dogs. LN extirpation in conjunction with chemotherapy was pursued in 4/12 dogs, and chemotherapy alone was pursued in 6/12 dogs. Five dogs received vinblastine 2.0 to 2.5 mg/m^2 ×8 doses with prednisone 0.5 to

Table 3. Lymph node histopathology for dogs with digital and distal limb cutaneous and subcutaneous mast cell tumours

Lymph node histopathology[a]	
Low-grade mast cell tumours (*n*=40)	
HN0	19/40
HN1	12/40
HN2	8/40
HN3	1/40
High-grade mast cell tumours (*n*=15)	
HN0	3/15
HN1	4/15
HN2	1/15
HN3	7/15
Subcutaneous mast cell tumours (*n*=3)	
HN0	0/3
HN1	1/3
HN2	1/3
HN3	1/3

[a]Lymph node histopathology is based on the Weishaar classification of nodal metastasis.

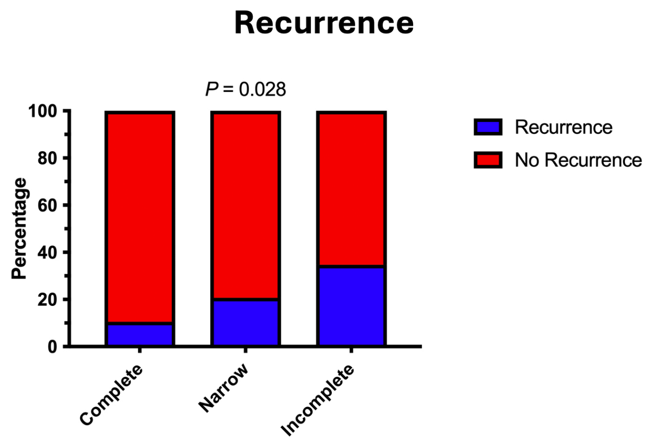

FIG 1. Bar graph demonstrating recurrence rate for mast cell tumours with complete excision (>5 mm), narrow excision (1 to 4 mm) and incomplete excision.

1 mg/kg PO q 24. Two dogs received CCNU 60 to 70 mg/m^2 ×4 doses with prednisone 0.5 to 1 mg/kg PO q 24. Three dogs received toceranib 2.2 to 3.25 mg/kg PO Monday, Wednesday and Friday.

Adjuvant therapy and adverse effects

Adjunctive treatment was performed in 30% of dogs (35/115) with scar revision performed in 1 dog, radiation therapy (RT) to the scar in 6 dogs, chemotherapy in 25 dogs and a combination of chemotherapy and scar revision in 3 dogs. Radiation protocols performed included 3.2 Gy × 15 fractions (3/6 cases), 3.2 Gy × 14 fractions, 3.2 Gy × 16 fractions and 3 Gy × 18 fractions (one case each). Recurrence was not documented in 5/6 dogs treated with RT. These dogs were monitored on an active monitoring plan, and no recurrence was seen after a median of 1,254 days post radiation (range: 38 to 2400 days). The single dog with recurrence occurred 89 days post RT with 3 Gy × 18 fractions. Twenty-eight dogs underwent adjunctive chemotherapy treatment. Most dogs (25/28) received vinblastine 2.5 mg/m^2 ×8 doses (range: 1.6 to 3.0 mg/m^2) with prednisone 0.5 to 1 mg/kg PO q24. One dog received CCNU dosed at 70 mg/m^2 ×6 doses, and two dogs received toceranib 2.2 to 3.25 mg/kg PO Monday, Wednesday and Friday long term. Nine dogs receiving vinblastine required dose reductions due to adverse effects.

Clinical outcome

Local recurrence occurred in 23% of dogs overall (27/115). Local recurrence occurred with surgical treatment alone in 66% of dogs (18/27), surgery and chemotherapy in 26% of dogs (7/27), surgery and radiation therapy in 4% of dogs (1/27) and surgery, chemotherapy and radiation therapy in 4% of dogs (1/27). The recurrence rate of Kiupel high-grade MCTs (50%) was significantly higher compared to Kiupel low-grade MCTs (15%) (P < 0.01). Recurrence was significantly more likely in MCTs with a mitotic count >5. MCTs with a mitotic count of >5 had a recurrence rate of 45% compared to a mitotic count ≤5 with a recurrence rate of 20% (P = 0.02). There was a significant difference between histological margins (complete, narrow and incomplete) and local recurrence (P < 0.02). Overall, 34% of dogs had a complete excision (39/115), 24% had a narrow excision (28/115) and 42% of dogs had an incomplete excision (48/115). Recurrence was least common with complete excision (10%), followed by narrow excision (20%), and most common with incomplete excision (35%) (Fig. 1). For marginal excision, only 9% of dogs had complete margins (4/47), 23% had narrow margins (11/47) and 68% had incomplete margins (32/47). The median time to local recurrence was 449 days (range: 38 to 2724 days). Recurrence occurred sooner with Kiupel high-grade MCTs, median of 300 days, compared to Kiupel low-grade MCTs, median of 500 days (P < 0.001). Kiupel high-grade MCTs were significantly more likely to recur with an odds ratio (OR) of 5.6 (P < 0.01) compared to Kiupel low-grade MCTs. Recurrence was seen in 25% (3/12) of subcutaneous MCTs. Recurrence was also associated with mitotic count, with a mitotic count of >5 having a 45% recurrence rate and a mitotic count of ≤5 having a 20% recurrence rate. A MCT with a mitotic count of >5 was significantly more likely to recur with an OR of 3.5 (P < 0.02) compared to a MCT with a mitotic count ≤5. Following initial diagnosis and surgical treatment of the digital MCTs, 15/115 dogs developed *de novo* MCT, which were diagnosed during follow-up visits with a median time to formation of 561 days (range: 55 to 2156 days). All dogs developing *de novo* MCTs had originally been diagnosed with a low-grade MCT.

The overall median PFI was 1,632 days (range: 30 to 4028 days). The median PFI for low-grade MCTs was 1,756 days and 888 days for high-grade MCTs (Fig. 2), and this difference was significant (P < 0.03). There was a significant difference in PFI based on the type of surgery performed, with wide excision having a longer PFI at 2,270 days and marginal excision having a shorter PFI at 888 days (Fig. 3) (P < 0.04). Mitotic count was significantly associated with PFI, with a mitotic count of ≤5 having a PFI of 1,667 days and a mitotic count of >5 at 256 days. MCTs with a mitotic count of >5 had a 2.3x increased risk of progression [hazard ratio (HR) (95% CI): 2.32 (0.953 to 5.686); P < 0.01], compared to MCTs with a mitotic count of ≤5.

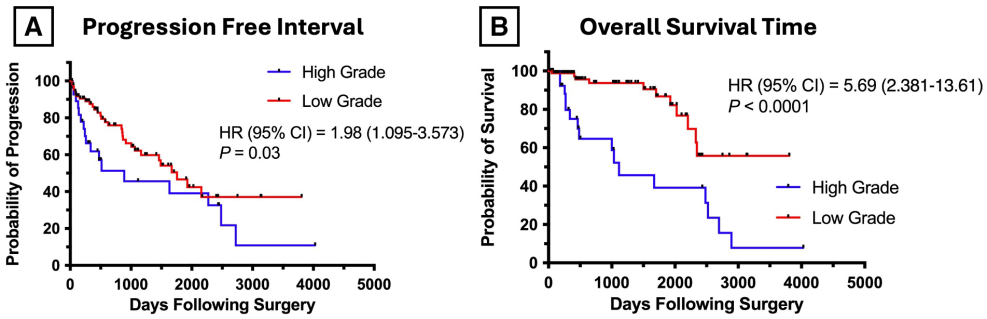

FIG 2. (A) Kaplan–Meier curves showing progression-free interval for low- and high-grade mast cell tumours. Dots on the curves represent censored patients. (B) Kaplan–Meier curves showing overall survival time for low- and high-grade mast cell tumours. Dots on the curves represent censored dogs.

High-grade MCTs had increased HR for tumour progression of 2x (HR [95% CI]: 1.98 (1.095 to 3.57); P < 0.03), compared to low-grade MCTs. Overall median PFI was not affected by regional LN status; however, LN status was only known for 58/115 cases. There was no significant difference in PFI for high-risk dogs (high-grade MCTs or HN3 LN) treated with chemotherapy *versus* those not treated with chemotherapy (P = 0.28) (Fig. 4). The median PFI for dogs with high-grade MCTs treated with chemotherapy was 1,632 days (range: 139 to 2724 days). The median PFI for dogs with high-grade MCTs not treated with chemotherapy was 334 days (range: 55 to 4028 days).

The median OST was 2,520 days (range: 30 to 3808 days). The median OST for low-grade MCTs was not reached and was 1,116 days for high-grade MCTs (Fig. 2). There was a significant difference in OST between low- and high-grade MCTs, with low-grade MCTs having a longer OST (P < 0.01). High-grade MCTs had a 5.6x increased risk of mortality [HR (95% CI): 5.69 [2.381 to 13.61]; P < 0.01], compared to low-grade MCTs. Mitotic count was significantly associated with OST, with mitotic count of ≤5 having an OST of 2,696 days and mitotic count of >5 at 1,000 days (P < 0.01). MCTs with mitotic count of >5 had a 3.4x increased risk of mortality [HR (95% CI): 3.415 (1.103 to 10.57); P < 0.01], compared to MCTs with mitotic count of ≤5. Median OST was not affected by regional LN status; however, LN status was only known for 58/115 dogs. The median OST for dogs with high-grade MCTs treated with chemotherapy was 1,671 days (range: 272 to 2894 days). The median OST for dogs with high-grade MCTs without chemotherapy was 484 days (range: 70 to 4028 days). Median OST was not affected by chemotherapy treatment for high-risk dogs (high-grade MCTs or HN3 LN) treated with chemotherapy (P = 0.61) (Fig. 4). Tumour location was not prognostic for outcome.

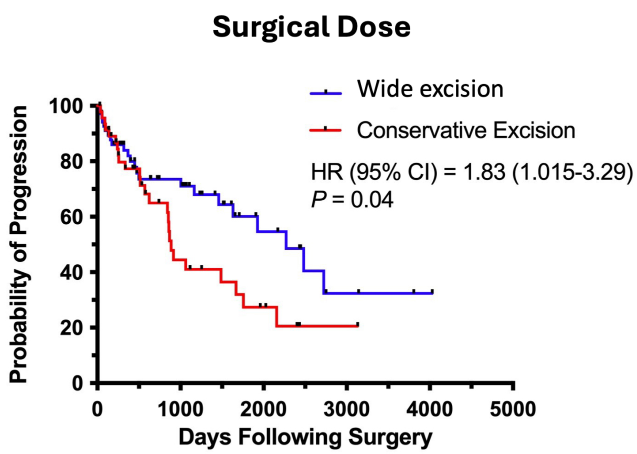

FIG 3. Kaplan–Meier curves showing progression-free interval for marginal excision compared to wide excision for digital and distal limb mast cell tumours. Dots on the curves represent censored dogs.

DISCUSSION

In this study, surgically treated digital and distal limb MCTs had an excellent outcome with a median OST of 7 years. This OST is similar to cutaneous and subcutaneous MCTs arising from non-high-risk locations (Gill et al., 2020; Horta et al., 2018). The biologic behaviour of digital and distal limb MCTs was predominantly based on tumour grade. This tumour location did not demonstrate inherently aggressive MCT behaviour similar to mucocutaneous junction locations of the prepuce, vulva or oral cavity (Thamm et al., 2006). However, no cases of subungual MCTs were available for inclusion, preventing the evaluation of a historically aggressive biologic behaviour and predisposition for nodal metastasis (London & Thamm, 2019; Marino et al., 1995; Wobeser et al., 2007). The median OST for surgically excised low-grade MCT on the digits and distal limb was not reached in this study, consistent with findings by Horta et al. (2018) and Sabattini et al. (2021). The median OST for surgically excised high-grade MCT of the digits and distal limb was 1,116 days, which is similar to prolonged survival times of 904 to 1,374 days seen in recent studies (Moore et al., 2020; Thamm et al., 2006). This is longer than historically reported median survival times for high-grade cutaneous MCTs of 108 to 331 days (Horta et al., 2018; Hume et al., 2011; Sabattini et al., 2021; Thamm et al., 2006).

Similar to OST for digital and distal limb MCTs, the median PFI was significantly longer for low-grade MCTs at 1,756 days compared to high-grade MCT at 888 days. Although a significant difference was found for PFI and OST for MCT grade, no

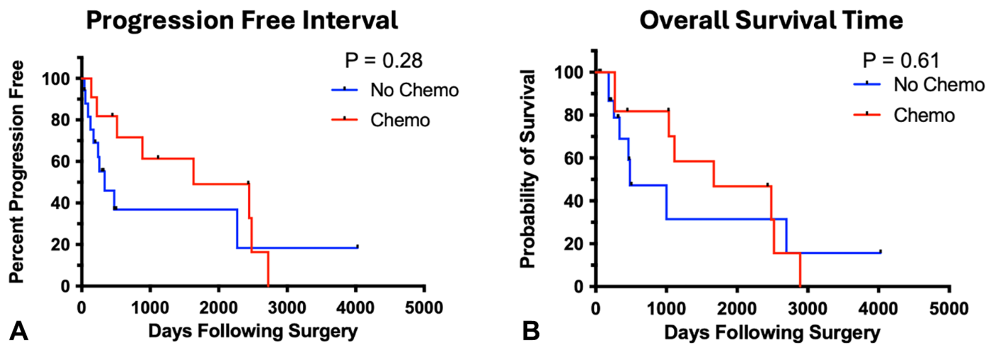

FIG 4. (A) Kaplan–Meier curves showing progression-free interval for dogs with high-risk mast cell tumours treated with or without chemotherapy. Dots on the curves represent censored dogs. (B) Kaplan–Meier curves showing overall survival time for dogs with high-risk mast cell tumours treated with or without chemotherapy. Dots on the curves represent censored dogs.

significant difference was found for LN status. This is consistent with findings by Guerra et al, supporting histological grade having more weight than positive nodal status as a predictor of outcome for cutaneous MCTs (Guerra et al., 2022). In contrast, other studies show an overtly metastatic LN (HN3) in conjunction with high-grade MCT as a negative prognostic indicator (Hume et al., 2011; Sabattini et al., 2021; Weishaar et al., 2014). However, recent studies demonstrate patients with an overtly metastatic LN in conjunction with a low-grade MCT may not be associated with tumour-related death (Sabattini et al., 2021; Stefanello et al., 2024).

Surgical approach had a profound impact on PFI, with wide excision (digit amputation, partial foot amputation, partial limb amputation or full limb amputation) having an extended median PFI of 2,270 days compared to marginal excision of 888 days. No significant difference was found for surgical approach and OST, which may be explained by owners pursuing additional treatments such as additional surgery or chemotherapy at the time of recurrence or could be attributed to type II error. This correlation of surgical dose and improved PFI has not been reported within veterinary MCT literature and suggests more complete resection may be beneficial to prolong PFI in canine MCT patients. These findings may be explained by the decreased recurrence rate seen with complete surgical margins and local recurrence having been associated with the progression of malignancy (O'Connell & Thomson, 2013; Séguin et al., 2006). Incomplete excision of digital and distal limb MCTs had the highest recurrence rate at 35% compared to narrow excision with a 20% recurrence and complete excision with a 10% recurrence rate. However, historically, tumour grade has been the most important predictor of local recurrence (Burge et al., 2023). Recurrence rates for high-grade cutaneous MCTs range from 13% to 75% and up to 35% with complete histological margins (Moore et al., 2020; O'Connell & Thomson, 2013; Saunders et al., 2021). In contrast, low-grade MCTs have low reported recurrence rates from 0% to 23% with the median time to local recurrence not being reached in many studies (Saunders et al., 2021; Séguin et al., 2006). In the current study, tumour grade was strongly associated with recurrence, with high-grade MCTs having a local recurrence rate of 50% compared to low-grade MCTs at 15%. This was further supported by an increased odds ratio of recurrence for high-grade MCTs, being 5.6 times more likely to recur than low-grade MCTs. Two cases had MCT recurrence at the surgical site at the time of tertiary referral following local surgical treatment with their primary veterinarian. The impact of local recurrence in this setting could not be assessed due to small case numbers.

Mitotic count was strongly associated with recurrence, with a mitotic count of >5 being 3.5x more likely to recur than MCTs with a mitotic count ≤5. An increasing mitotic count has been associated with MCT recurrence (Horta et al., 2018). Specifically, a mitotic count of >4 correlated with recurrence in subcutaneous MCTs (Thompson et al., 2011). Furthermore, an increasing mitotic count has been identified as a negative prognostic indicator contributing to decreased OST (Moore et al., 2020; O'Connell & Thomson, 2013; Romansik et al., 2007). The current study supports a mitotic count of >5 being associated with increased local recurrence rate and decreased PFI and OST. Dogs with MCT mitotic count >5 were 2.3x more likely to experience tumour progression and 3.4x more likely to experience MCT-related death.

Chemotherapy is often recommended with high-risk MCT disease (high-grade MCTs or HN3 LN) (Anderson et al., 2024; Stefanello et al., 2024; Thamm et al., 2006). However, many studies have not found a survival benefit for high-grade MCTs treated with chemotherapy (Burge et al., 2023; Moore et al., 2020; O'Connell & Thomson, 2013). Thamm et al. demonstrated an improved PFI in high-grade MCTs of 1374 days when treated with cytotoxic chemotherapy (vinblastine/prednisone) (Thamm et al., 2006). The current study showed a similarly prolonged PFI of 1632 days for high-risk dogs treated with cytotoxic chemotherapy (vinblastine/prednisone or CCNU/prednisone) compared to 334 days without. Although subjectively longer with chemotherapy treatment, a significant difference in PFI for high-risk dogs treated with chemotherapy was not shown. Thamm et al. concurrently demonstrated an apparent benefit of chemotherapy treatment improving OST in high-grade MCTs with 65% of cases alive at 1095 days (Thamm et al., 2006). The current study showed a similar increase in OST of 1671 days with chemotherapy treatment compared to 484 days without chemotherapy treatment. Although OST was subjectively improved with chemotherapy treatment, these findings were not statistically significant. The lack of significance for PFI and OST for treatment with chemotherapy in high-grade MCTs may be explained by type II statistical error stemming from the small sample size of dogs receiving chemotherapy ($n=28$), bias for more advanced cases with negative prognostic indicators receiving chemotherapy and inconsistent staging and follow-up. Furthermore, the authors acknowledge there may have been overtreatment with chemotherapy for dogs with low-grade MCTs with HN3 LN status as recent literature has demonstrated a favourable outcome for low-grade MCTs independent of LN status (Stefanello et al., 2024).

Diagnostics performed were variable with a lack of consistency for preoperative and postoperative staging, RLN sampling and follow-up. All owners were offered full staging at the time of MCT diagnosis. Many owners did not move forward with this recommendation due to cost. The authors recommend preoperative staging and either SLN mapping or extirpation of the RLN at the time of surgery as the gold standard for treatment for digital and distal limb MCTs. Only a small portion of dogs had digital radiographs as a component of initial work up (9/115). Digital radiographs did not show evidence of bony lysis in any case, which supports the tendency of MCTs to not infiltrate bone. This suggests distal extremity radiographs may not be beneficial for MCTs of the digits and distal limb.

As physical exam alone is not a sensitive method for detecting metastasis to LNs, cytology of RLN or SLN should be implemented for thorough staging (Langenbach et al., 2001). LN cytology and histopathological evaluation of the same LN were available in 60% of cases having had FNA performed (40/66). LN cytology for diagnosis of metastatic *versus* non-metastatic LN agreed with histopathology in 85% of cases (34/40). However, LN cytology should not replace histopathology as cytology cannot reliably predict LN HN status (Buzzi et al., 2023). The accuracy of cytology compared to histopathology is similar to Ku et al with 82% accuracy of cytologically diagnosed MCT LN metastasis (Ku et al., 2017). These findings are consistent with Warland et al. that demonstrated LN metastasis in 30% of cases at the time of cutaneous MCT diagnosis (Warland et al., 2014). Warland et al. also showed a consistent pattern of MCT metastasis from draining LN onto distant sites with no dog having distant metastasis in the absence of metastasis to draining LN (Warland et al., 2014). The current study showed a similar pattern of metastatic disease detected at follow-up with higher prevalence of LN metastasis in the RLN (16/24) than liver and spleen (5/24), with no dog having visceral metastasis detected prior to RLN metastasis. However, lack of standardised staging could have missed cases of distant metastasis as visceral metastatic rate has been shown to be higher in recent literature, especially in high-grade MCTs (Brown et al., 2022; Ribeiro et al., 2022). SLN mapping has been shown to be beneficial in recent studies as, although most cases of forelimb digital MCTs share a RLN and SLN of the superficial cervical LN, some have the axillary LN as the sentinel (Ferraris et al., 2023). This is similar to a distal hindlimb MCT with the majority sharing a RLN and SLN of the popliteal LN with some having the inguinal LN as the sentinel (Ferraris et al., 2023). Recent literature by Ferrari et al., Worley et al. and Lapsley et al. have demonstrated SLN using lymphography in dogs with MCT enhances detection of occult nodal metastasis and resulted in improved staging (Ferrari et al., 2020; Lapsley et al., 2021; Worley, 2014). In the current study, LN extirpation was not found to have benefit for PFI or OST. This contrasts with findings by Chalfon et al. which demonstrated increased PFI with regional lymphadenectomy for high-grade MCTs from 150 days to 229 days and median OST of 250 days to 371 days with lymphadenectomy (Chalfon et al., 2022). For head and neck MCTs, Marconato et al. showed not performing a lymphadenectomy for a metastatic LN was associated both with tumour progression and tumour-related death (Marconato et al., 2018). Mendez et al. found survival benefit for high-grade MCT with adjunctive LN treatment (extirpation or RT) with MST of 282 days without treatment and 483 days with treatment (Mendez et al., 2020). Lack of statistical significance for LN extirpation on PFI or OST in the current study may be explained by lack of SLN mapping, the majority of caseload being low-grade cutaneous or low biologic behaviour subcutaneous MCT and less than 1/2 of total cases undergoing LN extirpation.

De novo MCT formation was diagnosed in 13% of cases at follow-up. *De novo* MCT formation occurs in 8% to 30% of cases in the veterinary literature (Moore et al., 2020; Saunders et al., 2021). *De novo* MCT formation has not historically been associated with decreased OST (Mullins et al., 2006). However, it is challenging to know the true prevalence of *de novo* MCT formation compared to distant metastasis, as clonality of MCT was not assessed, as described by Zavodovskaya et al. (2004).

Limitations of this study include the retrospective nature, lack of standardised case management, tertiary caseload and non-standardised follow-up. Bi-institutional case collection was performed to gain a higher caseload for this uncommon digital tumour type. However, it introduced differences in data collection, follow-up and case treatment based on clinician discretion and varying institutional protocols. There was no control population, which prohibited evaluation for predisposing factors for digital and distal limb MCTs. No cases of subungual MCTs were found in this data series, limiting comparison to previous literature which suggested that this tumour location may have more aggressive biologic behaviour. Furthermore, preoperative staging was variable, with only 50% of cases undergoing presurgical staging, which varied significantly for diagnostics performed. The inconsistencies in staging could have led to lower detection for distant and LN metastasis and detection of metastasis to the liver and spleen. Furthermore, the MCT cytological scoring system described by Camus et al could have helped guide which patients were more likely to have high-grade MCTs and may have strongly benefited from preoperative staging (Camus et al., 2016). Potentially prognostic immunohistochemistry stains such as ki67 or AgNOR were also not evaluated in this study, which could have helped predict prognosis for MCT in this region (Smith et al., 2017). Unfortunately, no patient received SLN mapping in this study, making it impossible to know if the RLN was the true SLN that was sampled cytologically or surgically extirpated. This would have contributed to more accurate LN extirpation and more accurate depiction of LN metastasis, which may have changed treatment recommendations based on LN HN grade.

Furthermore, there were not enough cases to evaluate statistical significance for the effect of LN extirpation in dogs with LN metastasis. Another limitation is the lack of histological evaluation of all samples by a single pathologist. Alternate grading scales such as the R excisional margin or tangential margin classification were also not used in this study (Dores et al., 2018; Liptak, 2020). The authors acknowledge the shortcomings of margins being reported in millimetres, which can be affected by tissue contraction and processing along with the limitations of only using the radial margin technique. However, a lower recurrence rate has been reported in soft tissue sarcoma for a narrow (close but complete margin) than for an incomplete incision, highlighting a potential advantage to the radial technique method for margin reporting (Chiti et al., 2021). Additionally, follow-up was variable, and most patients did not receive consistent continued staging for their lifespan. Due to inconsistencies in restaging, our case numbers have inherent bias and may not reflect the true PFI of this population. Although not evaluated with force plate analysis, subjectively, dogs did very well with digit and full limb amputation. This information could have provided more objective measurements to assess changes in gait and mobility postoperatively (Fuchs et al., 2014; Sellon et al., 2021). Lastly, the majority of dogs did not have a necropsy performed, which may have decreased the true prevalence of metastasis, local recurrence and *de novo* MCT formation.

In conclusion, the overall outcome with surgical excision is excellent, with median OST of 7 years for all cases. Low-grade MCT cases had an excellent outcome, with median OST not being reached, and high-grade MCT cases having MST of more than 3 years. The behaviour of MCT on the digits and distal limb seems to be affected primarily by tumour grade. Improved PFI occurred with wide excision (digit amputation, partial foot amputation, partial limb amputation and full limb amputation) compared to marginal excision. Recurrence rates were highest in cases with high-grade MCT, incomplete surgical resection and mitotic count of >5. Future studies are needed to further evaluate the effects of adjuvant chemotherapy, metastatic LN status and LN extirpation in high-grade MCT cases.

Author contributions

A. K. Erickson: Conceptualisation; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **G. Tremolada:** Conceptualisation; investigation; methodology; writing – review and editing. **D. H. Thamm:** Methodology; data curation; formal analysis; writing – review and editing. **B. D. Husbands:** Conceptualisation; investigation; methodology; writing – review and editing.

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Conflict of interest

The authors do not have a conflict of interest for this study.

Data availability statement

Research data are not shared.

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