Mast Cell Tumors

Prioritizing Treatment in General Practice

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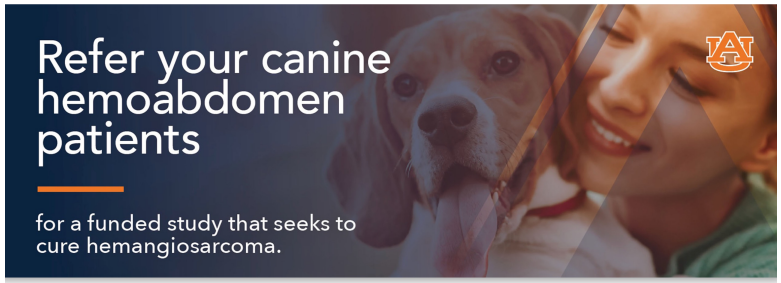


Auburn Oncology is happy to partner with Ethos Discovery as a site in the Southeast for their clinical trial for canine hemangiosarcoma. New data, including over 190 prospectively evaluated dogs with hemoabdomen, indicates there is more hope than you may think for your patients:

Ethos-PUSH Study

Any dog with a hemoabdomen secondary to a ruptured splenic mass	Exclusions: pulmonary metastasis, concurrent cancer, DCM, IRIS stage 2+ CKD
Patients must be enrolled PRIOR TO splenectomy, which must be performed at Auburn University	
Initial participation is just allowing extra samples to be collected	Blood, urine, effusion, feces, histopathology $1,000 surgical discount
Phase 2: dogs with HSA are randomized to 1 of 4 treatment arms	Free drug, monitoring, imaging

Outline

- Practical staging
- Surgery and grade assessment
- Adjuvant therapy or in lieu of surgery

Introduction

- 20% of cutaneous tumors in dogs
- Variety of presentations

London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition, edited by Vail DM, Thamm DH, Liptak JM. 382-403. Missouri: Elsevier, 2020

Easy Prognostic Factors

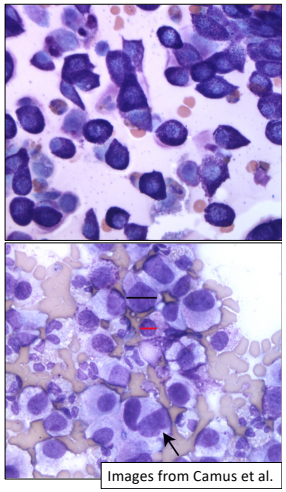
- Breed
- Tumor size and growth rate
- Anatomic location
- Recurrence
- Local signs
- Systemic signs (rare)

London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition, edited by Vail DM, Thamm DH, Liptak JM. 382-403. Missouri: Elsevier, 2020

Cytology

- Main route for diagnosis
- May suggest grade[1]

High grade if:		
Poor granulation	OR	At least 2 of the following: • Presence of mitotic figures • Binucleation/multinucleation • Nuclear pleomorphism • >50% anisokaryosis

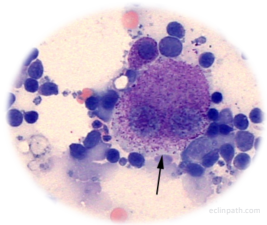


Images from Camus et al.

[1] Camus MS, et al. Cytologic criteria for mast cell tumor grading in dogs with evaluation of clinical outcome. *Vet Path.*

Biologic Behavior

- EXTREMELY variable
- Lymphatic metastasis
  - Lymph node → spleen, liver → other sites
  - 20-30% LN metastasis at diagnosis
  - Palpably normal LN: 22% metastatic[1]



- Extirpation of metastatic LN reduces risk of recurrence and metastasis[2]
- *How do we identify the draining lymph node?*

[1] Ferrari R, et al. Assessing the risk of nodal metastasis in canine integumentary mast cell tumors: is sentinel lymph node biopsy always necessary? *Animals (Basel).*
[2] Marconato L, et al. Therapeutic impact of regional lymphadenectomy in canine stage II cutaneous mast cell tumours. *Vet Comp Oncol.*

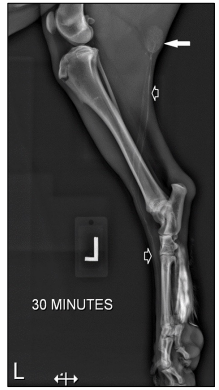
Sentinel Lymph Node (SLN) Mapping

- Lymphoscintigraphy[1]
  - 8 dogs (42%) had different SLNs than expected
  - 12 dogs (63%) had nodal metastasis (mostly low-grade tumors)
- Indirect CT lymphography[2]
  - SLN was <u>not</u> the locoregional lymph node in 28%
  - 9/20 SLN had metastasis vs. 1/20 locoregional LN
- **Changed the treatment plan in 41%**[1,2]

[1] Worley DR. Incorporation of sentinel lymph node mapping in dogs with mast cell tumours: 20 consecutive procedures. *Vet Comp Oncol.*
[2] Lapsley J, et al. Influence of locoregional lymph node aspiration cytology vs sentinel lymph node mapping and biopsy on disease stage assignment in dogs with integumentary mast cell tumors. *Vet Surg.*

Is There an Easier Way?

- *Can we use indirect lymphography with digital radiographs and aqueous contrast?*
- Pilot study[1]
  - Healthy dogs
  - Injected iopamidol in standard location at the tarsus
  - Successful in 7/8 dogs

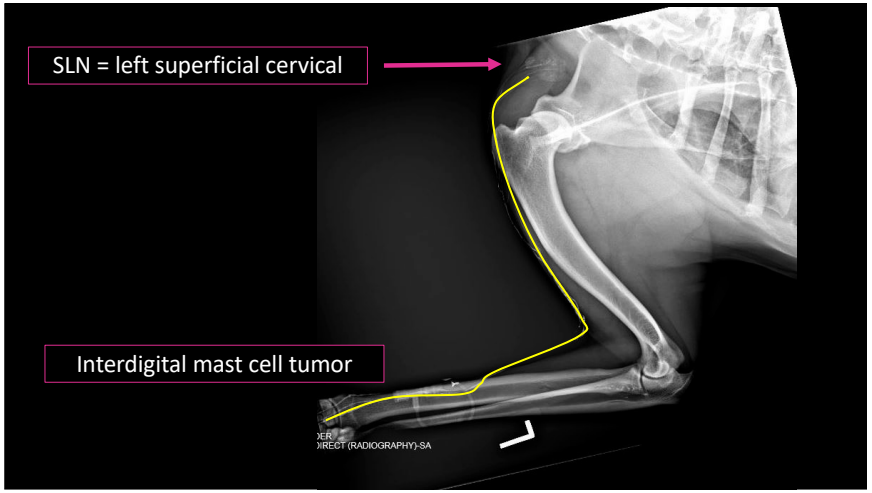


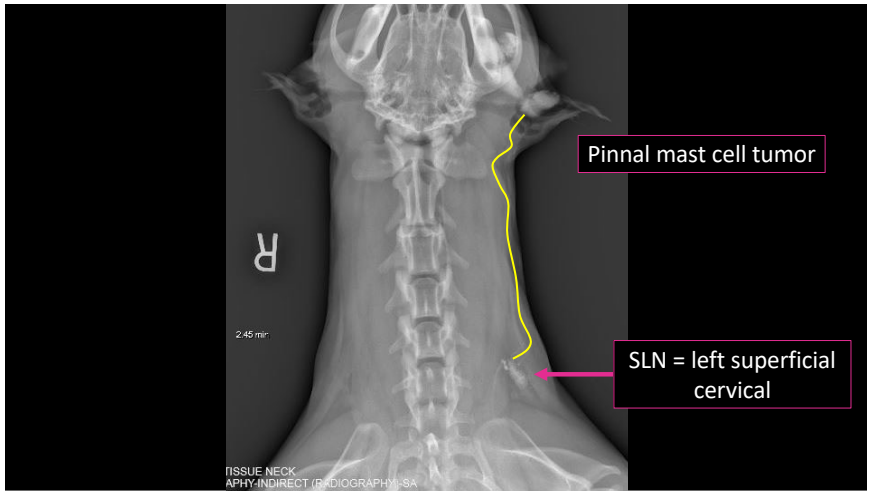
[1] Hlusko KC,, et al. Sentinel lymph node detection differs when comparing lymphoscintigraphy to lymphography using water soluble iodinated contrast medium and digital radiography in dogs. *Vet Radiol Ultrasound.*

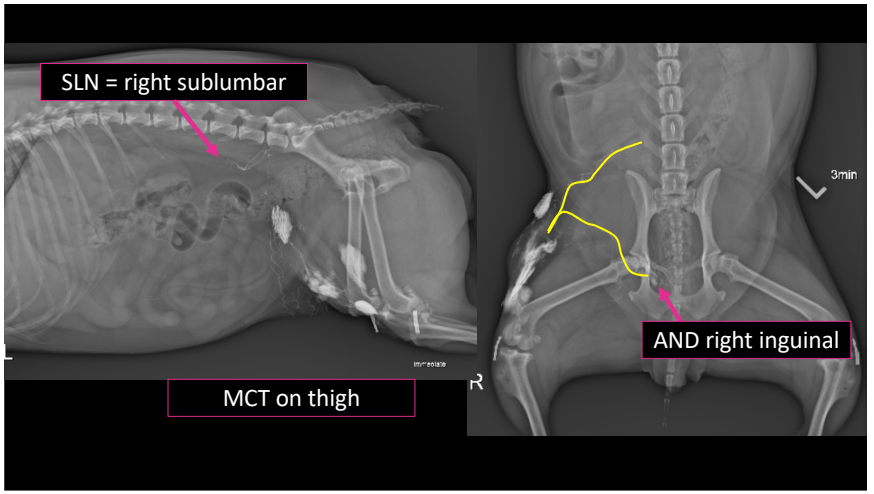
AU Indirect Lymphography Protocol

- Light sedation
- 4 mL iopamidol in 4 quadrant peri-tumoral pattern → gently massage
- Survey radiographs → repeat immediately after → once per minute
  - Ultrasound used to aspirate if needed (63%)
- 78% good or adequate results (46/59)
  - Timing: 41% immediate
  - Remaining mean 3.5 minutes

Haas S, et al. Indirect lymphography for sentinel lymph node detection in dogs with mast cell tumors. *Can Vet J.*







Feasibility of Indirect Lymphography

Limitations	Advantages

• Requires 4 mL
  • Challenging locations
• Failure in 22%
  • Torso more difficult
  • **CT lymphography** more sensitive
• SLN may change post-op
	• Readily available
	• Quick
	• Affordable
	• Identifies the majority of SLNs
	  • Excellent for head, neck, and extremities
	• **Monitoring of SLN post-treatment**

Additional Staging Diagnostics

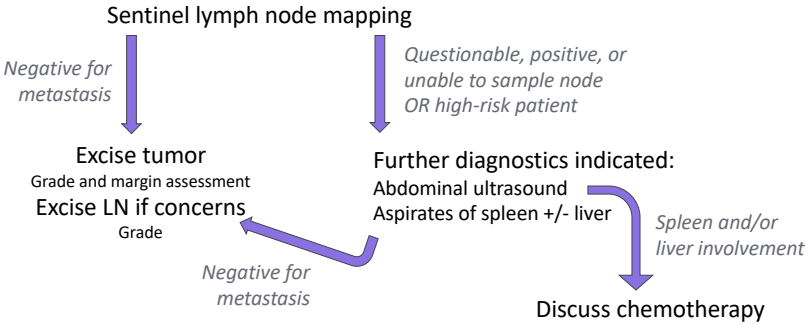
- Minimum database + thoracic radiographs (wellness)
- Abdominal ultrasound with spleen +/- liver aspirates
  - Low rate of metastasis (0.7-6.8%)[1,2]
  - Appearance not predictive[3]
  - Splenic cytology (vs. both) may be sufficient[4]
- Consider for high-risk dogs → esp. rapid growth and grade III[5]

[1] Rinaldi V, et al. The role of fine needle aspiration of liver and spleen in staging of low-grade canine cutaneous mast cell tumor. *Vet Sci.*
[2] Warland J, et al. The utility of staging in canine mast cell tumours. *Vet Comp Oncol.*
[3] Pecceu E, et al. Ultrasound is a poor predictor of early or overt liver or spleen metastasis in dogs with high-risk mast cell tumours. *Vet Comp Oncol.*
[4] Brown M, et al. Utility of spleen and liver cytology in staging of canine mast cell tumors. *J Am Anim Hosp Assoc.*
[5] Fejos C, et al. Extensive staging has no prognostic value in dogs with low-risk mast cell tumours. *Vet Comp Oncol.*

Mast Cell Tumor Trafficking

- 1/4 normal lymph nodes contain mast cells
  - Consider SLN extirpation
- Trafficking through spleen and liver
  - Cytologic criteria?
  - Clinical picture

Proposed Approach to Staging



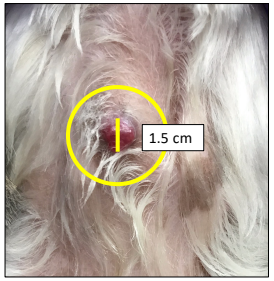
Corticosteroids and Anti-Histamines

- At risk patients
- Prednisone: cytotoxic or anti-inflammatory?
  - Pre-treatment did not significantly change histopathology results[1]
- Diphenhydramine has variable bioavailability in dogs[2]
  - **Cetirizine** (2 mg/kg PO q 12 hr)[3]

[1] Linde KJ, et al. The effect of prednisone on histologic and gross characteristics in canine mast cell tumors. *Can Vet J.*
[2] Ehling S, et al. Diphenhydramine pharmacokinetics after oral and intravenous administration of diphenhydramine and oral administration of dimenhydrinate to healthy dogs, and pharmacodynamic effect on histamine-induced wheal formation: a pilot study. *Vet Dermatol.*
[3] Banovic F, et al. Effect of diphenhydramine and cetirizine on immediate and late-phase cutaneous allergic reactions in healthy dogs: a randomized, double-blinded crossover study. *Vet Dermatol.*

Surgical Margins

- **Tumors < 2 cm:** proportional lateral margins and 1 fascial plane deep
- **Tumors > 2 cm:** 2-3 cm lateral margins and 1 fascial plane deep
- Proportional vs. 3 cm margins (low-grade tumors)
  - 92-95% completely excised[1,2]
  - 3% recurrence[2]
- Cryotherapy?



[1] Chu ML, et al. Comparison of lateral surgical margins of up to two centimeters with margins of three centimeters for achieving tumor-free histologic margins following excision of grade I or II cutaneous mast cell tumors. *J Am Vet Med Assoc.*
[2] Saunders H, et al. Evaluation of a modified proportional margins approach for complete surgical excision of canine cutaneous mast cell tumours and its association with clinical outcome. *Vet Comp Oncol.*

Scar Line Cytology Predicts Recurrence

- *When to treat incompletely excised low-grade tumors?*
  - FNA scar at suture removal and rechecks
- Negative predictive value: 93.5%
- Cytologic residual disease = 22X higher risk of recurrence

Predictive ability of fine-needle aspirate cytology for incompletely resected mast cell tumor surgical sites

Christopher E. Lee, Stephanie S. Lindley, Annette N. Smith, Philippe Gaillard, Ralph A. Henderson, Brad M. Matz

Canadian Veterinary Journal, 2021

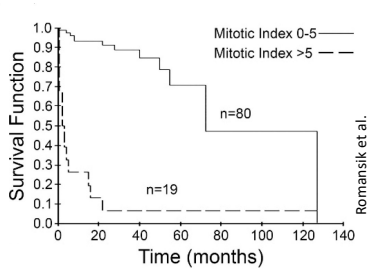
Histologic Grading Schemes

- Grade = most consistent and reliable prognostic factor
  - Patnaik grades I, II, and III
- Variable grade II behavior → utility of Kiupel system

London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition.

Mitotic Index is Independently Prognostic

- 96% specific at predicting MCT-related death
  - ≤ 5 → MST 5.8 years
  - > 5 → MST 2 months
- Poor sensitivity



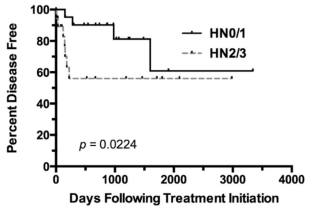
Romansik EM, et al. Mitotic index is predictive for survival for canine cutaneous mast cell tumors. *Vet Pathol.*

Mast Cell Tumor Prognostic Panel

- Ki-67, AgNORs, c-Kit PCR (ITD in exons 8 and 11), KIT IHC
- Consider additional therapy for low-grade tumors:
  - High proliferation index
  - Exon 11 ITD
  - Aberrant KIT expression

Lymph Node Grade Impacts Prognosis

Classification	Histopathologic Criteria	Proposed Interpretation
HN0	None to rare (0-3) mast cells per x400 field	Non-metastatic
HN1	>3 individualized mast cells in a minimum of 4 x400 fields	Pre-metastatic
HN2	Aggregates (clusters, > 3) of mast cells	Early metastasis
HN3	Disruption or effacement of architecture	Overt metastasis



Lymph Node Grade	DFI	Median OST (Years)	2-Year Disease Free
HN0 or HN1	NR	5 years	90%
HN2 or HN3	NR	2.2 years	56%

Weishaar KM, et al. Correlation of nodal mast cells with clinical outcome in dogs with mast cell tumour and a proposed classification system for the evaluation of node metastasis. *J Comp Pathol.*

Incompletely Excised Mast Cell Tumors

- Additional local control dictated by grade, scar line cytology, recurrence
- Scar revision[1]
  - 27% had residual disease
  - 4% recurrence
- Definition radiation therapy[2]
  - Include SLN
  - 7% recurrence
- Electrochemotherapy?
  - Median DFS > 4 yr

[1] Karbe GT, et al. Evaluation of scar revision after inadequate primary excision of cutaneous mast cell tumors in 85 dogs (2000-2013). *Vet Surg.*
[2] Mason SL, et al. Outcomes of adjunctive radiation therapy for the treatment of mast cell tumors in dogs and assessment of toxicity: A multicenter observational study of 300 dogs. *J Vet Intern Med.*

Low-Grade, Non-Metastatic MCTs

- Likely do well regardless of margin status
  - Only 20% recur
- Consider mitotic index and prognostic panel for low-grade, grade II
- Active surveillance
  - Scar line cytology
  - Sentinel lymph node cytology
  - +/- full staging?

Low-Grade MCTs with Nodal Metastasis

- Treatment dictated by grade
  - HN0 or HN1 → active surveillance
  - **HN3** → chemotherapy
- HN2 lymph nodes?
  - Unknown utility of chemotherapy[1]

[1] Marconato L, et al. Adjuvant medical therapy provides no therapeutic benefit in the treatment of dogs with low-grade mast cell tumours and early nodal metastasis undergoing surgery. *Vet Comp Oncol.*

High-Grade Mast Cell Tumors

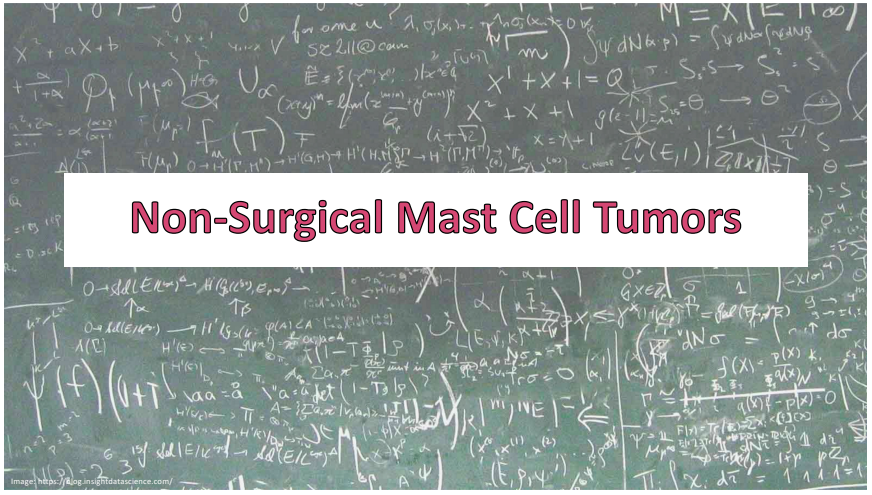
- **Chemotherapy** indicated!
- Up 90% will die from their disease
  - ~40% recurrence
  - 55-96% metastasis

London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition.

Post-Operative Chemotherapy

- Vinblastine/prednisone
  - "High-risk" MCTs = MST 3.7 years
- Currently no data for microscopic disease
  - Palladia®
  - Chlorambucil

London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition.



Non-Surgical Mast Cell Tumors

- Neoadjuvant therapy? Marginal excision?
- Radiation therapy
- Chemotherapy
- Stelfonta®
- Electrochemotherapy

Palladia® and Hypofractionated Radiation Therapy

- 76-87% overall response rate
  - 67% complete response
  - Median PFS: 10.5 months
- Side effects?
  - Radiosensitizer

Published in final edited form as:
J Vet Intern Med. 2012 ; 26(1): . doi:10.1111/j.1939-1676.2011.00851.x.

Multicenter Prospective Trial of Hypofractionated Radiation Treatment, Toceranib, and Prednisone for Measurable Canine Mast Cell Tumors

K.S. Carlsten, C.A. London, S. Haney, R. Burnett, A.C. Avery, and D.H. Thamm

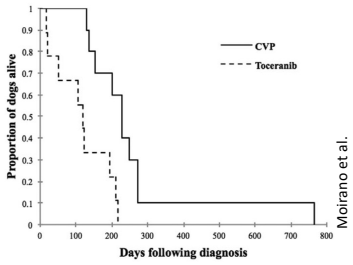
Carlsten KS, et al. Multicentric prospective trial of hypofractionated radiation treatment, toceranib, and prednisone for measurable canine mast cell tumors. *J Vet Intern Med*.

Chemotherapy for Measurable MCTs

- Vinblastine
- CCNU
- Vinblastine/CCNU alternating
- Vinblastine/cytoxan
- Chlorambucil
- Hydroxyurea
- Palladia®
- Palladia®/vinblastine
- Palladia®/CCNU
- Masitinib
- Imatinib

CCNU-Based Protocols

- CCNU/prednisone
- CCNU/vinblastine/prednisone
  - Stage IV disease[1]
- Neutropenia, hepatotoxicity



Moirano et al.

[1] Moirano SJ, et al. Association of prognostic features and treatment on survival time of dogs with systemic mastocytosis: A retrospective eanalysis of 40 dogs. *Vet Comp Oncol.*

Palladia® (toceranib phosphate)

- Recurrent or metastatic, intermediate- or high-grade tumors
  - Better response if c-kit mutation?
- Adverse events @ labeled dose[1]
  - Diarrhea (46%)
  - Neutropenia (46%)
  - Anorexia (39%)
  - Vomiting (32%)
  - Elevated liver enzymes (24%)
  - Others

→

- **2.4-2.9 mg/kg PO EOD**[2]
  - Sufficient for [VEGF] inhibition
- Substantial reduction in side effects

[1] London CA, et al. Multi-center, Placebo-controlled, Double-blind, Randomized Study of Oral Toceranib Phosphate (SU11654), a Receptor Tyrosine Kinase Inhibitor, for the Treatment of Dogs with Recurrent (Either Local or Distant) Mast Cell Tumor Following Surgical Excision. *Clin Cancer Res.*
[2] Bernabe LF, et al. Evaluation of the adverse event profile and pharmacodynamics of toceranib phosphate administered to dogs with solid tumors at doses below the maximum tolerated dose. *BMC Vet Res.*

Palladia® Considerations

- Unknown utility in microscopic disease
- Side effects
- Cost
- Exposure to client
- **Alternate days with NSAIDs or steroids**

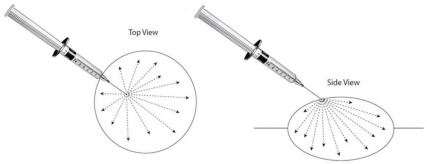
Palladia® in Multi-Drug Protocols

- Cytotoxic drug requires dose reduction
- Vinblastine: 1.6 mg/m^2
- *Pulse-dosed* with CCNU: 50 mg/m^2
  - Standard dose: 100% "unacceptable toxicity" 30% mortality

Bavcar S, et al. Combination toceranib and lomustine shows frequent high grade toxicities when used for treatment of non-resectable or recurrent mast cell tumours in dogs: A European multicentre study. *Vet J.*

Stelfonta® (tigilanol tiglate)

- Cell death and vascular dysfunction
- Non-metastatic MCTs < 10 cm^3
  - If SC, must be below the elbow or hock
- Pretreat with corticosteroids and anti-histamine
- Website assists in dose calculation



Source: Stelfonta® product insert

Picture 1. Thirteen days after self-injection

Stelfonta® product insert

Recommended PPE:
- Gloves
- Eye protection
- Lab coat or gown

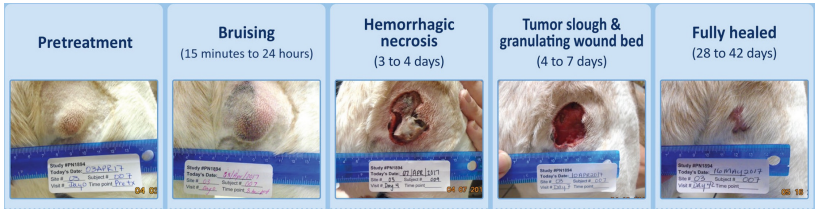
Stelfonta® (tigilanol tiglate)

- 75% CR after 1 treatment, 88% after 2[1]
- Dogs achieving CR: 89% tumor-free at 1 year[2]
  - 11% recurrence, mostly within first 3 months
- Cytologically high-grade tumors less likely to respond[1]
  - Also avoid in dogs with nodal metastasis

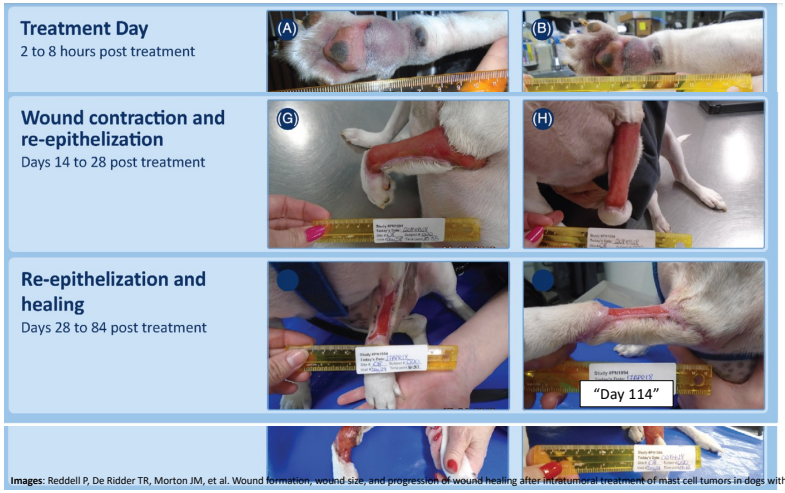
[1] De Ridder TR, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). *J Vet Intern Med.*
[2] Jones PD, et al. Recurrence-free interval 12 months after local treatment of mast cell tumors in dogs using intratumoral injection of tigilanol tiglate. *J Vet Intern Med.*

Stelfonta® (tigilanol tiglate)

- 95% acute tissue necrosis and wound formation
  - May last up to 3 months
- Injection site pain, lameness in treated leg, GI upset, degranulation



De Ridder TR, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). *J Vet Intern Med.*



Images: Reddell P, De Ridder TR, Morton JM, et al. Wound formation, wound size, and progression of wound healing after intratumoral treatment of mast cell tumors in dogs with tigilanol tiglate.

Image: https://magazine.columbia.edu/article/best-way-stop-negative-thought-spiral

Dependent on Tumor Grade

- Non-metastatic grade I and grade II, low grade
- Grade II, high-grade
  - 14-56% die of disease → chemotherapy
  - MST 7-23 months?
- Grade III
  - 75% die of disease → chemotherapy
  - Median 3-7 months?

Willmann M, et al. Proposed Diagnostic Criteria and Classification of Canine Mast Cell Neoplasms: A Consensus Proposal. *Front Vet Sci.*

The Outliers…

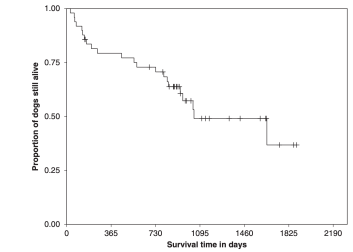
ORIGINAL ARTICLE

Veterinary and Comparative Oncology WILEY

Retrospective outcome evaluation for dogs with surgically excised, solitary Kiupel high-grade, cutaneous mast cell tumours

Antony S. Moore[1] | Angela E. Frimberger[1] | David Taylor[2] | Neill Sullivan[3]

- n=49 high-grade MCTs
  - SX: most complete margins
  - 67% adjuvant chemotherapy
- 18% recurrence, 12% nodal metastasis
- MST 2.8 years
  - Neg px = LN metastasis



Subcutaneous Mast Cell Tumors

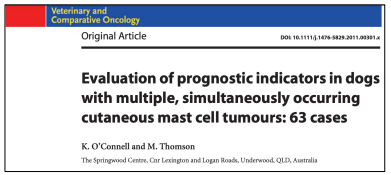
- Grade does not apply
- Lower risk of metastasis (4-27%) and recurrence (8-18%)[1,2]
- Negative prognostic indicators
  - Mitotic index > 4
  - Multinucleation
  - Infiltrative growth pattern

  → MST 140 days if all present[1]
  - Lymph node metastasis → MST 1.5 years[3]
- Median PFS 4 years, MST > 5.4 years[3]

[1] London CA and Thamm DH. "Mast Cell Tumors." Withrow & MacEwen's Small Animal Clinical Oncology 6th edition.
[2] Cherzan NL, et al. Factors affecting prognosis in canine subcutaneous mast cell tumors: 45 cases. *Vet Surg.*
[3] Gill V, et al. Prognostic Indicators and Clinical Outcome in Dogs with Subcutaneous Mast Cell Tumors Treated with Surgery Alone: 43 Cases. *J Am Anim Hosp Assoc.*

Multiple Cutaneous Mast Cell Tumors

- May vary in grade (33%)
- Associations
  - Atopic dermatitis (improved PFS)
  - Tumors > 3 cm
  - Grade III tumors
- Median PFS and OST not reached
  - How to treat?


Veterinary and Comparative Oncology

Original Article

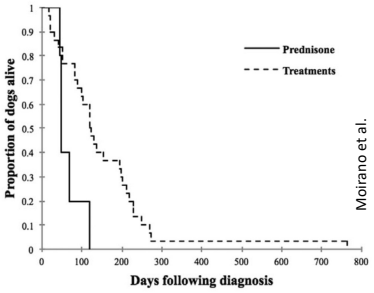
Evaluation of prognostic indicators in dogs with multiple, simultaneously occurring cutaneous mast cell tumours: 63 cases

K. O'Connell and M. Thomson

The Springwood Centre, Cnr Lexington and Logan Roads, Underwood, QLD, Australia

Stage IV Disease

- MST 3-4 months with treatment[1]
  - Palliative w/ steroids: 49 days[2]
- Chemotherapy improves survival[2]
  - 47% response rate[1]
  - CCNU/VBL vs. Palladia®



Moirano et al.

[1] Moirano SJ, et al. Association of prognostic features and treatment on survival time of dogs with systemic mastocytosis: A retrospective analysis of 40 dogs. *Vet Comp Oncol.*
[2] Pizzoni S, et al. Features and prognostic impact of distant metastases in45 dogs with de novo stage IV cutaneous mast cell tumours: a prospective study. *Vet Comp Oncol.*

Conclusions

- Variable behavior, but all are capable of lymphatic metastasis
  - Staging guided by patient risk factors, consider SLN mapping
- Histologic grade is the most important prognostic factor
  - Incompletely excised, low-grade tumors may be cured
  - High-grade tumors need chemotherapy
- Various chemotherapy options exist, no one-size-fits-all
- Very little absolutes about prognosis, except for stage IV disease