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Abstract

Mast cell tumors (MCTs) are common cutaneous neoplasms in dogs. This article discusses recent updates in the management of mast cell disease, specifically the use of the MCT prognostic panel; evaluation of regional and sentinel lymph nodes for the presence of metastasis; and local and systemic treatments, including novel therapeutics such as tigilanol tiglate injection and gilvetmab. Ideal scenarios for prognostic panel use and an overview of the implications of lymph node metastasis for survival and systemic therapy are also provided.



ONCOLOGY

Simplifying the Approach to Canine Mast Cell Tumors

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Mast cell tumors (MCTs) are common cutaneous neoplasms in dogs. As treatment recommendations and prognostic factors for MCTs continually change, this article aims to demystify the clinical approach to MCTs by reviewing indications for use of the MCT prognostic panel, the clinical relevance of regional lymph node metastasis, and various local and systemic therapies.

USE OF THE MCT PROGNOSTIC PANEL

An MCT prognostic panel is available through

IDEXX and the Michigan State University Veterinary Diagnostic Laboratory. This multifaceted panel is a valuable tool for further characterizing cutaneous and subcutaneous MCTs with equivocal histopathology. The panel includes proliferative indices, *c-kit* mutation status (exons 8 and 11), and KIT localization pattern. These findings are most informative when considered together rather than individually.^{1,2}

For histologically high-grade MCTs, the information gained from the prognostic panel

Take-Home Points

- The mast cell tumor (MCT) prognostic panel is useful in guiding treatment recommendations for histologically low-grade MCTs with equivocal histologic features or clinical history concerning for aggressive behavior.
- While detecting metastatic lymph nodes can be challenging, addressing metastatic lymph nodes through surgery or radiation can improve survival. In certain cases, addressing the metastatic lymph node may eliminate the recommendation for systemic therapy.
- Local therapy for MCTs includes surgery, radiation therapy, electrochemotherapy, and intralesional agents. Tigilanol tiglate injection is an intralesional treatment that causes wound formation, which, in rare cases, can be extensive.
- Proportional surgical margin recommendations appear adequate for achieving local control of low-grade MCTs up to 2 cm in diameter.
- Some options for systemic therapy for MCTs are cytotoxic chemotherapy, tyrosine kinase inhibitors, a new checkpoint inhibitor (gilvetmab), and/or corticosteroids. Additional supportive care most often includes histamine antagonist and/or proton pump inhibitor medications.



may not change treatment recommendations. The authors feel this tool is best employed when the clinician has reason to suspect that an initial interpretation of low grade is incorrect.

Possible indications for MCT prognostic panel use include:

- Low-grade tumors in breeds predisposed to high-grade tumors (e.g., Chinese Shar-Pei; **FIGURE 1**)³
- Low-grade tumors with conflicting history (e.g., rapid growth, ulceration, edema, systemic illness consistent with degranulation)²
- Low-grade tumors in concerning anatomic locations (e.g., perioral, ear base, nail bed, other mucocutaneous sites, inguinal/perineal, preputial/scrotal)³⁻⁵
- Low-grade tumors with contradictory histopathologic features (e.g., borderline mitotic count [4 to 8/10 high-power fields], low mitotic count with concurrent marked multinucleation/nuclear atypia)⁶

IMPORTANCE OF LYMPH NODES

Detecting metastatic lymph nodes presents a challenge, as not all lymph nodes can be palpated or identified as abnormal via physical examination or imaging. For



FIGURE 1. A female Chinese Shar-Pei with diffuse mast cell disease 1 month after presenting for a solitary mast cell tumor.

BOX 1 Weishaar's Histologic Classification System for Lymph Node Metastasis in Canine Mast Cell Tumors¹⁰

HN0: Nonmetastatic

HN1: Premetastatic

HN2: Early metastasis

HN3: Overt metastasis

example, 50% of palpably normal lymph nodes were found to contain metastasis in a population consisting of 90% low-grade tumors.⁷ Furthermore, the regional (nearest) lymph node is not always the sentinel (draining) lymph node. A recent study using lymph node mapping found that regional and sentinel lymph nodes differed in nearly 60% of MCT cases.⁸

While the presence of lymph node involvement is used to stage MCTs (**TABLE 1**), MCT lymph node metastasis is not histologically classified as a “yes/no” binary. Instead, Weishaar's histologic classification system assesses the number, distribution, and architectural disruption of mast cells within a lymph node (**BOX 1**).¹⁰ This classification describes the extent of nodal metastasis and is increasingly provided on biopsy reports. One study found a difference in survival between patients with HN0 + HN1 lymph nodes (60 months) and those with HN2 + HN3 lymph nodes (27 months).¹⁰ This study included all tumor grades. A more recent study that focused on grade II/low-grade MCTs with HN2 metastasis found that these patients experienced prolonged survival with surgery alone, with median survival time not reached (median follow-up time, 750 days), suggesting early lymph node metastasis (HN2) is insufficient to warrant systemic treatment.¹¹

Histologic tumor grade is more predictive of patient outcome than lymph node status; however, a common thread has emerged over the past decade: Treatment of metastatic lymph nodes has a more significant impact on patient survival than the presence of lymph node metastasis.¹²⁻¹⁴ Treatment can include extirpation, chemotherapy, and/or radiation therapy.

Patients with lymph node involvement (stage II) that do not undergo extirpation have a 5-fold increased risk of tumor progression and a 4-fold increased risk of



tumor-related death.¹³ Among patients with grade II (intermediate) MCTs, survival is unaffected by lymph node metastasis (stage I versus stage II), assuming the lymph node is removed. Extirpation permitted patients a median survival time of “not reached” (median follow-up time, 409 days) compared with a median survival time of 360 days in patients in which the metastatic lymph node was not removed (median follow-up time, 620 days) in 1 study.¹³

The value of treating affected lymph nodes is not exclusive to intermediate-grade MCTs. In dogs with high-grade MCTs, prophylactic irradiation of regional lymph nodes resulted in significantly increased progression-free survival compared with those that did not have lymph node extirpation or irradiation.¹⁴

LOCAL THERAPY

Surgery

Surgery is considered the gold standard for MCT treatment and is often curative. While recommended surgical margins of 3 cm laterally and 1 fascial plane deep were previously applied to all MCTs, recent studies have suggested this may be more tissue than needed to achieve adequate local control of many MCTs.¹⁵⁻¹⁷ Since most MCTs are low grade and dogs experience low recurrence rates, even with incomplete histologic margins, a smaller surgical dose may be sufficient.¹⁷

Several updated recommendations have been proposed. Most prominent is the use of proportional margins. In this approach, a 0.5-cm mass would be removed with 0.5-cm lateral margins, a 1-cm mass with 1-cm margins, and so on up to 2 cm. The recommendation of removing 1 fascial plane deep remains. With this approach, 95% of MCTs were completely excised (all margins histologically clear of mast cell infiltration), regardless of grade, with an overall recurrence rate of 3% in 1 study.¹⁷ Despite the active components of mast cell granules, these patients do not experience increased incision site complications compared to those with soft tissue sarcomas.¹⁸

With recurrence rates for incompletely excised, low-grade tumors at 10% to 30%, several follow-up options exist.^{15,17,19} These may include active surveillance for tumor regrowth, scar revision, or radiation therapy. Scar revision can improve long-term survival (from 24 to 98 months) and decrease recurrence rates (from 38% to 13%).²⁰

Tumor grade and stage may alter the decision to proceed with surgery and associated surgical dose. Cases with negative prognostic factors (see **Use of the MCT Prognostic Panel**) should undergo complete staging preoperatively. This includes cytologic evaluation of regional (ideally sentinel) lymph nodes and the spleen (plus or minus the liver).^{8,21} Since ultrasonography has poor sensitivity and specificity in identifying MCT metastasis in the liver and spleen, percutaneous fine-needle aspiration with cytologic evaluation is recommended regardless of the

TABLE 1 World Health Organization Clinical Staging System for Canine Cutaneous Mast Cell Tumors⁹

STAGE	DESCRIPTION
0	One tumor incompletely excised from the dermis, identified histologically, without regional lymph node involvement a. Without systemic signs b. With systemic signs
I	One tumor confined to the dermis, without regional lymph node involvement a. Without systemic signs b. With systemic signs
II	One tumor confined to the dermis, with regional lymph node involvement a. Without systemic signs b. With systemic signs
III	Multiple dermal tumors; large infiltrating tumors with or without regional lymph node involvement a. Without systemic signs b. With systemic signs
IV	Any tumor with distant metastasis, including blood or bone marrow involvement



ultrasonographic appearance of these organs. While uncommon, viscerally disseminated disease has a considerable impact on expected survival and may alter the decision to proceed with surgery.²¹

Radiation Therapy

Radiation therapy has been used in the adjuvant setting following incomplete resection or in the gross tumor setting for nonresectable tumors.^{14,20} The long-term benefits of radiation therapy for high-grade tumors remain unclear, although radiation therapy is an effective means for reducing the recurrence of low-grade MCTs. A recent study of predominantly low-grade MCTs treated with radiation therapy following incomplete excision demonstrated a recurrence rate of less than 7% and tumor-specific survival time that was not reached.²²

Acute toxicity (adverse effects seen during radiation therapy or within 2 weeks of completion) can be seen in MCT patients with gross or microscopic disease. These effects include erythema, desquamation, or other adverse events outlined in the modified Veterinary Radiation Therapy Oncology Group scoring criteria.^{22,23} Concurrent use of supportive medications, particularly prednisone, histamine H₁ and H₂ antagonists, or proton pump inhibitors, can help decrease the severity of adverse events.²²

Intralesional Therapy

Triamcinolone

Triamcinolone is a long-acting steroid that can be administered intralesionally to decrease or maintain MCT size. In 1 study of 23 dogs, the overall response rate (complete and partial responses) was 67%, including patients receiving concurrent therapies. For patients treated with triamcinolone with or without oral corticosteroids, the median time to progression was 28 days and 114 days, respectively. The most common adverse effects were gastrointestinal (GI) upset and bleeding at the injection site, which was suspected to be related to degranulation. This therapy is economical and does not require special equipment or training, although the duration of response appears limited.²⁴

Tigilanol Tiglate Injection

Tigilanol tiglate injection (Stelfonta; Virbac, [stelfonta.com](https://www.stelfonta.com)) is an intralesional treatment labeled for canine

cutaneous and subcutaneous MCTs that received full U.S. Food and Drug Administration approval in 2020. Tigilanol tiglate injection uses a multimodal mechanism of action, including causing tumor cell oncolysis, activating an acute inflammatory response, and increasing tumor vascular permeability. Ultimately, tigilanol tiglate injection results in tumor necrosis and

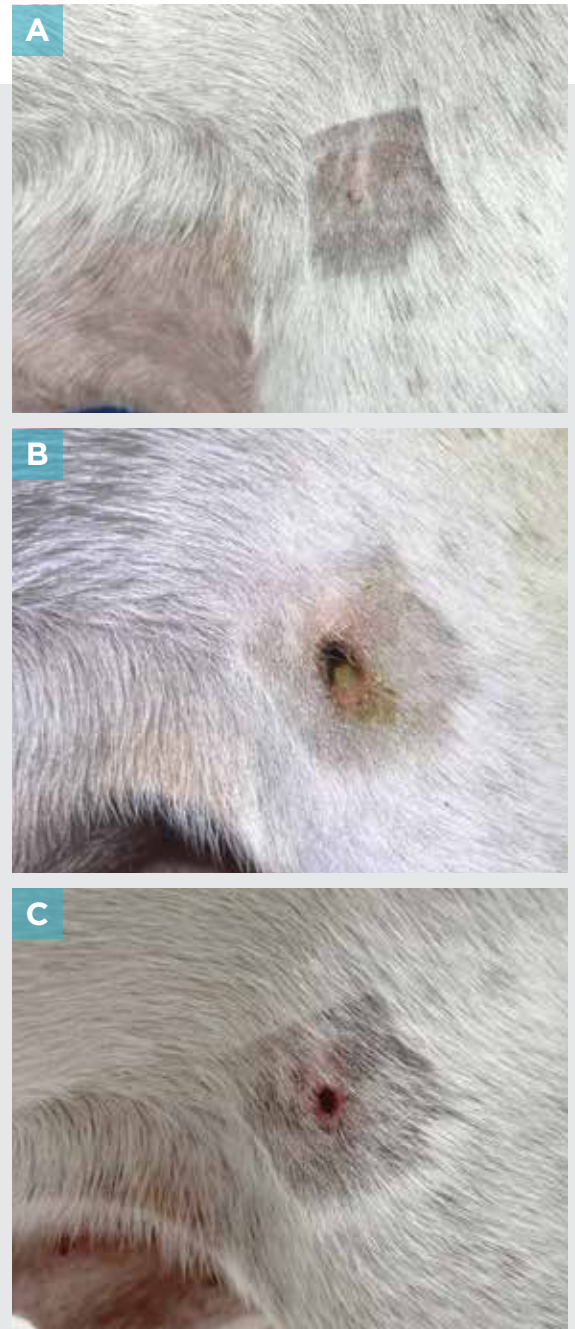


FIGURE 2. Cutaneous mast cell tumor on the left lateral thigh (A) immediately before, (B) at 7 days after, and (C) at 14 days after tigilanol tiglate injection administration.



tissue sloughing, resulting in wound formation at the tumor site (FIGURE 2).²⁵

Corticosteroids and H₁ and H₂ antagonists are initiated in advance and at the start of treatment. Tigilanol tiglate injection should be handled using personal protective equipment. Dose calculation is based on tumor volume, which is labeled for tumors less than 10 cm³. The dose is labeled not to exceed 0.25 mL/kg or 5 mL/dog. Using a 23-g needle, a single insertion site is made at the base of the tumor and the drug is administered in a fanning motion to maximize drug delivery. It is recommended to sedate patients to improve drug delivery and decrease the risk of accidental needlesticks to the administrator.²⁵ The authors use Kevlar gloves to increase administrator protection.

Proper case selection and client education are crucial. Tigilanol tiglate injection is labeled for use in nonmetastatic MCTs. Cutaneous MCTs can be located anywhere, but subcutaneous MCTs must be distal to the elbow or hock to reduce peritumoral tissue damage. Clients should be prepared for wound formation and associated healing times. Tumor size is often similar to wound size, which correlates with healing time. While most patients experience expected wounds, rare instances (2%) experience extensive wound formation. Wound formation peaks at 7 days and typically heals by weeks 4 through 6. Unless purulent material is noted or a patient is traumatizing the area, wound care, bandaging, antibiotics, and Elizabethan collars are unnecessary. Local pain is usually well controlled with analgesics for about 1 week in 63% of patients.²⁵

Tigilanol tiglate injection is an exciting new tool, as most responders have significantly smaller wounds than the 2- or 3-cm margins that were previously recommended with surgery. Approximately 75% of patients (predominantly with cytologically low-grade tumors) had a complete response after 1 treatment. This increases to nearly 90% with inclusion of dogs that received a second treatment. Cytologically high-grade tumors have a lower complete response rate: 44% after 1 treatment and 67% after 2 treatments.^{26,27} Of patients with cytologically high-grade tumors that respond to tigilanol tiglate injection, approximately 70% remain disease-free at 1 year.²⁵ It is important to note that cytologic grading is not widely accepted, and a limitation of tigilanol tiglate injection treatment is the inability to obtain a histopathologic grade to better estimate prognosis.²⁶

SYSTEMIC THERAPY

Chemotherapy

Chemotherapy can be used as a neoadjuvant, adjuvant, or sole therapy for MCTs. In the neoadjuvant setting, chemotherapy and/or steroids can be used to reduce tumor size and facilitate surgery (also referred to as downstaging). Care should be taken when interpreting margins after neoadjuvant therapy since this approach is used to allow for marginal excision in challenging anatomic locations.²⁸ No studies have evaluated the effects of neoadjuvant chemotherapy on histologic grade or proliferation indices; however, neoadjuvant steroid therapy is unlikely to alter these values.²⁹

As an adjuvant treatment, chemotherapy has demonstrated substantial benefit in delaying metastasis in patients with high-grade MCTs.³⁰ Without systemic treatment, most dogs succumb to progressive or metastatic disease within 1 year. Chemotherapy can improve this time to more than 2 to 3 years.⁴ Fortunately, adjuvant chemotherapy is unnecessary for most patients with low-grade MCTs based on low metastatic and recurrence rates.¹³

The most common chemotherapy drugs used for MCTs are vinblastine and lomustine (CCNU [cyclohexylchloroethylnitrosourea]). Chemotherapy can be used in single-agent or multiagent protocols or in combination with prednisone.^{4,30-32}

Toceranib Phosphate and Other Tyrosine Kinase Inhibitors

Toceranib phosphate (Palladia; Zoetis, [zoetis.com](https://www.zoetis.com)) and other tyrosine kinase inhibitors (TKIs), such as masitinib mesylate (Masivet; AB Science, [masivet.co.uk](https://www.masivet.co.uk)) and imatinib mesylate (Gleevec; Novartis, [gleevec.com](https://www.gleevec.com)), have been used in MCT treatment.³³⁻³⁵ Responsiveness to TKIs is independent of *c-kit* mutation status. However, higher response rates occur in patients with *c-kit* mutations. Ultimately, *c-kit* mutation status should not limit treatment with TKIs if clinically warranted.³⁶

TKIs can be combined with radiation therapy and/or traditional chemotherapy in gross or microscopic disease settings, although this may increase adverse events. Toceranib phosphate is currently the only TKI labeled for canine MCT treatment in the United States. Imatinib mesylate is predominantly used to treat chronic myelogenous leukemia in humans and may be



more affordable than toceranib phosphate for large dogs. Overall response rates for TKIs range from 30% to 60% with variable progression-free intervals.³³⁻³⁵

Patients receiving TKIs should be monitored closely for adverse effects and disease progression. The most common adverse events include GI upset, anorexia, and weight loss.³³⁻³⁵ Additional side effects are unique to each TKI. Serious adverse events seen with toceranib phosphate may also include increased liver enzymes, proteinuria, hypertension, and GI bleeding.^{33,36,37} Due to these risks, the authors recommend consultation with a veterinary oncologist before prescribing TKIs.

Checkpoint Inhibitors

Gilvetmab (Merck, [merck-animal-health-usa.com](https://www.merck-animal-health-usa.com)) is a checkpoint inhibitor that received U.S. Department of Agriculture conditional approval for use in canine MCTs (stage I, II, or III) and melanoma (greater than 2 cm with or without lymph node involvement) in October 2023. Numerous canine tumors express programmed cell death ligand 1, which binds to programmed cell death 1 (PD-1) on tumor-infiltrating lymphocytes to evade destruction.³⁸ Gilvetmab is a caninized PD-1 monoclonal antibody that binds PD-1 on lymphocytes, thus enabling T lymphocytes to recognize tumor cells and promote cell killing.³⁹

Gilvetmab is given as an intravenous infusion repeated every 2 weeks for up to 10 treatments. It has an overall response rate of 46% in canine patients with MCTs. As with many immunotherapies, patients should be monitored for pseudoprogression, a phenomenon whereby tumor size increases due to resurgent inflammation. This local growth can be misinterpreted as treatment failure and may result in premature treatment discontinuation. Pseudoprogression can postpone tumor shrinkage by 8 to 12 weeks.³⁹

The manufacturer recommends pretreatment with diphenhydramine and reports the most common adverse effects as lethargy, hyporexia, and increased alkaline phosphatase. Approximately 11% of patients with MCTs have severe to life-threatening adverse events. The most concerning events include anaphylaxis, hypotension, and tumor hemorrhage. As gilvetmab is an immunotherapeutic treatment, it is not recommended for patients receiving chronic glucocorticoids or other immunosuppressive drugs. Clinical trials are ongoing.³⁹

Corticosteroids

Prednisone and other steroids have been shown to have inhibitory effects on mast cell viability and proliferation.⁴⁰ They can also decrease clinical signs associated with degranulation, such as edema, pruritus, and pain. Like chemotherapy, steroids can be used as a neoadjuvant, adjuvant, or sole therapy. While single-agent corticosteroids are economical and accessible, response is often short-lived at a few weeks. Anecdotally, neoadjuvant steroids achieve maximal response within 7 to 14 days; therefore, surgical excision should be scheduled during this timeframe.²⁹

SUPPORTIVE CARE

Dogs with MCTs are at risk for degranulation and increased plasma histamine concentrations, which lead to local and systemic effects such as changes in tumor size, wheal formation, GI upset/ulceration, anaphylaxis, and even death. As such, many veterinarians utilize over-the-counter histamine antagonist drugs to decrease the signs associated with mast cell degranulation and hyperhistaminemia.⁴¹ While H₁ antagonists (e.g., diphenhydramine) can limit cutaneous inflammation, H₂ antagonists (e.g., famotidine) are more important as about 30% of dogs with MCTs have evidence of GI ulceration at necropsy.⁴¹ The authors rely on H₂ antagonists for most cases, although for dogs with high disease burden (e.g., large, weeping tumors; disseminated metastasis), the authors switch to proton pump inhibitors (e.g., omeprazole) for more targeted blockade and long-term efficacy.⁴² Once microscopic disease is achieved, histamine antagonists and/or proton pump inhibitors can be discontinued.

SUMMARY

The diagnostic and therapeutic approach to canine MCTs has undergone several recent advances. The MCT prognostic panel is useful in guiding treatment recommendations, particularly in patients with histologically low-grade tumors with conflicting information. There is no singular test that can perfectly predict the behavior of a tumor; rather, results should always be interpreted in the context of clinical and diagnostic findings. Furthermore, the removal of metastatic lymph nodes significantly improves survival, even if systemic treatment is not warranted. MCTs can be managed with local and/or systemic treatment. With the broad range of MCT behavior and as treatment options evolve, veterinarians should reach out to veterinary oncologists as needed for support. **TV**



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