DIAGNOSIS AND TREATMENT OF CANINE MAST CELL TUMORS IN 2024: LATEST ADVANCES

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Mast cell tumors (MCT) represent a significant concern in veterinary oncology as the most prevalent cutaneous neoplasm affecting our canine companions, comprising 16 to 21% of all skin tumors diagnosed in dogs. The crux of successful intervention lies in the timely detection and the strategic approach of initial fine-needle aspirates prior to any surgical removal. The management of MCT underscores the heterogeneity - no single therapeutic strategy applies universally. Remarkably, a spectrum of MCT, specifically those classified as low to intermediate grade, hold a promising prognosis with comprehensive surgical excision or Stelfonta®, often resulting in a cure. In contrast, the high-grade counterparts of this malignancy can be more aggressive, with a reduced survival to a mere three to six months if left untreated. Yet, the situation is not devoid of hope, as even high-grade MCT with metastatic spread remain amenable to intervention. Documented advancements in survival rates are a testament to the efficacy of aggressive combined modality treatments, incorporating both local control and systemic therapy, particularly for dogs bearing high-grade MCT and a high mitotic index. Understanding the biological behavior of mast cell tumors across the spectrum—from low to high grade—is crucial in devising effective treatment plans. By tailoring our approach to the individual characteristics of each tumor, we can offer more accurate prognoses and improve therapeutic outcomes, reinforcing the notion that MCT, regardless of their grade, are a manageable and treatable canine cancer.

PROGNOSTIC FACTORS:

Work up and treatment decisions can be considered based on the presence or absence of negative prognostic factors and the clinical stage of disease. Remember, prognostic factors cannot predict an individual's response. There are many prognostic factors, but the more significant predictors include:

- Histologic grade
- Stage
- Mitotic index: Mitotic Index is an indirect measure of cell proliferation based on number of mitotic figures and is a strong prognostic factor. It can be performed during routine histology. Look for this on your biopsy report. MI has been associated with metastasis and survival (but not recurrence)
- C-kit mutation
- MCT panel score which includes C-kit mutation and other proliferation markers that require additional immunohistochemical staining such as AgNOR and Ki-67
- Others include size, location, recurrence, clinical signs

WORKUP

Cytology: Skin and SQ masses should always be aspirated and examined cytologically. "See Something Do Something. Why Wait? Aspirate.®" (SSDS) provides guidelines for evaluating superficial masses in dogs and cats. These guidelines will increase client awareness and will promote early cancer detection, diagnosis, and early surgical intervention. In veterinary medicine, most skin and subcutaneous tumors can be cured with surgery alone if diagnosed early when tumors are small. See Something: When a skin mass is the size of a pea (1 cm) and has been present for at least 1 month, Do Something: Aspirate or biopsy, and treat appropriately.

Cytologic grading:

Traditionally, grading of mast cell tumors (MCT) requires biopsy and histopathology. However, MCT can be graded with cytology. Advantages include aspirates can be done more quickly, inexpensively, and less invasively than biopsy. There are a few recent publications that show high sensitivity and specificity. In the Camus study of 152 dogs, a cytologic grading scheme was created based on correlation with histologic grade.[3] A MCT was high grade if it was poorly granulated or had at least 2 of 4 findings: mitotic figures, binucleated or multinucleated cells, nuclear pleomorphism, or >50% anisokaryosis. The cytologic grading scheme had 88% sensitivity and 94% specificity relative to histologic grading. Dogs with histologic and cytologic high grade MCTs were 39 times and 25 times more likely to die within the 2-year follow-up period, respectively, than dogs with low grade MCTs. High tumor grade was associated with increased probability of additional tumors or tumor regrowth. This study concluded that cytologic grade is a useful predictor for treatment planning and prognostication. I recommend you request this from your cytologist, especially when treating with STELFONTA®. Other situations where cytologic grading can be helpful include preparing for surgery and planning margins, to guide staging before treatment, and setting owner expectations about recommendations and prognosis.

Staging: MCT metastasis is typically to local lymph nodes, liver, spleen, and/or bone marrow. Historically preoperative diagnostics have included a long list of tests. Staging diagnostics may include local lymph node fine needle aspirate, CBC, chemistry panel, urinalysis, abdominal ultrasound +/- liver and splenic aspirates. It is currently though that an extensive workup is not needed in most cases, unless the dog has negative prognostic factors. More recently, the importance of sampling draining lymph nodes for staging has been defined. There are a few different ways to predict the draining lymph node. At minimum, FNA for cytology of the draining lymph node should be performed for staging MCT. Non-palpable/normal-sized regional lymph nodes in dogs with MCT can harbor metastatic disease in nearly half of the cases. Extirpation of the regional lymph node can be considered to obtain a correct stage of the disease, even in the absence of clinical suspicion of metastasis.
Buffy coat is not recommended as this has a high false-positive rate. Thoracic radiographs are of limited usefulness in terms of staging for MCT but can be considered for general health screening.

The biopsy report: The report should be evaluated for grade, completeness of margins and mitotic index. Histologic grade is prognostic for biologic behavior and clinical outcome, and an accurate predictor for metastatic behavior. The classic grading system is **3-tiered**. Grade 1 MCT have a <10% metastatic rate. For intermediate grade/grade 2, the metastatic rate is low to moderate. But for grade 3 MCT, the metastatic rate is 55-96%. Unfortunately, there is inter-observer variation among pathologists, and pathologists tend to opt for grade 2 when it is borderline between grade 1 and 2. If more pathologists are calling tumors grade 2, the prognostic value is weakened. Based on the original work by Patnaik, there is ~ 50/50 chance of 5-year survival for grade 2 tumors. A **2-tiered system** had been developed and is based on the number of mitoses (< or > 7), presence of multinucleated cells or bizarre nuclei, and karyomegaly (increased nuclear size). High-grade tumors are significantly associated with shorter time to metastasis, mast cell tumor associated mortality, shorter overall survival time. MST for high-grade MCT < 4 months vs. > 2 years for low-grade MCT. Ideally you should be getting both grades in your histology reports. For incomplete margins post-operative options include scar revision (second surgery), external beam radiation therapy, chemotherapy, or monitoring. This emphasizes the need for early detection and identification of what the mass is prior to resection, so the first surgery can be curative intent surgery.

TREATMENT
Treatment of MCT can vary from simple and straightforward to complicated and controversial. Treatment decisions are often based in the clinical stage (presence of regional and/or distant metastasis) and the presence of prognostic factors. Surgical resection with clean and wide margins is recommended, but questions often arise in determining which dogs need chemotherapy post-operatively.

Surgery: Surgery is traditionally the first line of treatment for MCT and often the ideal treatment in areas amenable to wide resection. The majority of naïve dermal MCT are intermediate or low grade and will be cured with surgery alone, provided site is amenable. The surgical removal of MCT can be further described by the intended surgical dose. The options for surgical dose include marginal, planned narrow, and wide traditional margins (including proportional margins).

A **wide excision** involves removing the tumor with a margin of normal tissue and is considered the curative approach for MCT. The recommendations for amount of normal tissue to be removed varies.The traditional recommendations for margins have historically been 3 cm laterally and one fascial plane but this was largely anecdotal. **Proportional margins** are another acceptable version of a wide surgery and involve removing a rim of normal tissues that is equal to the diameter of the tumor plus one fascial plane. Proportional margins have been studied in MCT up to 5 cm in diameter and clean margins were obtained in 98% of dogs using this surgical approach. A recent study showed 0% recurrence rate in low grade (grade 1 and grade 2/low) MCT resected with proportional margins. In one study of 132 MCT treated with proportional margins, 95% of the margins were clean and the recurrence rate was 3%. All of the recurrent tumors in that study were high grade, two of which had clean margins. Therefore, 2 cm lateral margins may be adequate for most small and lower grade (grade 1 and grade 2) MCT with 1 fascial plane deep (proportional margins).

A **marginal excision** involves removing the entire mass with no surrounding normal tissue. Marginal excision can be defined as the removal of a tumor on or just outside the pseudocapsule/grossly visible tumor. “Marginal excision” is frequently used as a synonym for excisional biopsy. The main benefit of this surgical dose is that the remaining wound is small and closure options may be more straightforward compared to with the other surgical doses. The main downside of this surgical dose is that the margins are likely to be incomplete.

A **planned narrow excision** involves removing the entire mass with removal of as much of the tumor and surrounding tissues as possible within the constraints of the anatomical location, while maintaining a tension-free primary wound closure. This surgical dose has been recently described with moderately good success.

Frustratingly, histologic assessment of margins may be unreliable. Not all incompletely resected MCT will recur. In some studies, only 20 to 36% with incomplete margins recur. Additionally, recurrence in dogs with clean margins has been reported to be 5 to 37%. Note that microscopic formalin-fixed parameters do not reflect margin size at surgery. Tissue shrinkage of up to 30% for cutaneous tissues occurs. Tumor grade is an important prognostic indicator for local recurrence and likely to be more important than histological margins.

There are many different approaches to the surgical management of MCT. It is helpful to weigh the pros and cons of each surgical dose option in each individual case and considering the anatomic area. When considering challenging surgical locations such as the distal limb, wide clean margins are often not possible. In my opinion, amputation is probably too aggressive, and Stelfonta® can be considered in this location (see below).

With any surgery, complications are possible. In the largest most recent study of MCT removal, incisional complications were recorded for 40 of 293 (14%) tumors, (29/40 [73%] were minor complications and 11 [28%] were major complications). The most common complications are dehiscence (typically due to tension, infection, motion), infection, seroma, tumor regrowth. Complications have been associated with incomplete margins, larger tumors, higher grade MCT and post-operative chemotherapy administration.

For cases in which histologic margins are incomplete, additional local therapy such as radiation is recommended post-operatively. For incomplete margins post-operative options include scar revision depending on location (second surgery), external beam radiation therapy, chemotherapy, or monitoring. Although recurrence rates vary by study and incomplete resection does not always cause tumor regrowth, several studies have demonstrated a worse prognosis including decreased overall survival times and/or increased local recurrence rates, so I do advise owners of these risks associated with recurrence.

Radiation therapy (RT): Radiation is recommended when wide surgical excision is not feasible. MCT are responsive to radiation. Monotherapy has varying control rates with reported 1-year control rates of 50%. However, a better approach is often surgery with adjuvant radiation. First surgery is performed to achieve microscopic disease (clinical stage 0) followed by full course radiation therapy. A typical course of radiation is 15 treatments over 3 weeks and has high control rates of 85-95% 2-year control rates for grade 1 and 2 MCT. For macroscopic MCT, the combination of steroids with palliative radiation has been reported to have an improved overall response rate (ORR) of 75%. Palliative radiation is typically weekly radiation for 4 weeks.

STELFONTA®: STELFONTA® (tigilanol tiglate injection) is approved by the FDA as a prescription intratumoral injection indicated for the treatment of nonmetastatic cutaneous mast cell tumors and nonmetastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock. Tigilanol tiglate is part of a novel small molecule class of drugs called epoxy-tiglianes. It is isolated from the seed of *Fontainea picrosperma* (blushwood tree). It is its unique mode of action that sets it apart from other local treatment therapies.

STELFONTA® Mode of Action: The intratumoral injection of STELFONTA has three interrelated effects responsible for its anti-tumor properties. The first effect is oncolysis of tumor cells that come into direct contact with the drug. This occurs predominantly along the needle tracks during fanning of the drug within the tumor. This effect is noted within hours and is the effect of disruption of mitochondria and tumor cell membranes leading to necrosis. Second, the drug activates protein kinase C (PKC) β-II isoforms in the tumor endothelial cells. This affinity for β-II isoforms is highly specific and results in increased vasculature permeability and loss of tumor vasculature integrity. This results in the treated tumor having a bruised appearance within hours of the injection. Thirdly, STELFONTA activates a PKC signaling cascade throughout the mass resulting in an acute inflammatory response. The tumor and immediate surroundings develop swelling and erythema. The inflammatory response usually resolves in 2-4 days. Importantly, this inflammation actively leads to restriction of blood and oxygen supply to the tumor and recruitment of innate immune cells which target the tumor mass. These effects have a cumulative effect of necrosis of the tumor mass followed by slough of the tumor within 3-14 days. The induction of an innate immune response plays an antimicrobial role and initiates downstream cytokine signaling that contributes to subsequent initiation of wound healing at the site of necrotic tumor slough. STELFONTA has demonstrated direct effects on keratinocyte and fibroblast function via production of cytokines and chemokines that are associated with promotion of wound healing at the treatment site. Complete healing of the wound following tumor necrosis and slough occurs in most patients within 4-6 weeks.

Among dogs treated with STELFONTA®:

- 75% of mast cell tumors achieved resolution of the target tumor with just one treatment.
- 87% of dogs achieve resolution of the target tumor 28 days after either the first or 28 days after a second treatment.
- 12 weeks after a single injection, 96% of dogs remained disease free at the site of the treated tumor.
- In 98.2% of cases, full healing was observed within 3 months (bandaging, use of Elizabethan collars and topical or systemic antibiotics were only needed in rare circumstances)
- Most wounds were completely re-epithelialized within 28 to 42 days of treatment, with good cosmetic outcomes.
- The treatment is generally well-tolerated and does not adversely affect quality of life.
- The disease-free interval at the treatment site for patients treated in clinical trials is 89% at one year.

STELFONTA® Indications: STELFONTA® (tigilanol tiglate injection) is indicated for the treatment of non-metastatic canine mast cell tumors. Tumor volume should not exceed 10 cm^3. For cutaneous MCT, the MCT can be located anywhere on the body. For subcutaneous MCT, the MCT must be located at or distal to the elbow or the hock. STELFONTA should not be injected into ***subcutaneous*** mast cell tumors located above the elbow or hock (e.g., on the body, head, or neck) as this may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation.

STELFONTA® Four Stages of Treatment: It is best to think of STELFONTA treatment in four stages – concomitant medications, STELFONTA injection, tumor destruction and tumor site healing.

Stage 1 - Concomitant medications – pretreatment:

- This is an essential element of the protocol directed at decreasing the risk associated with mast cell tumor degranulation.
- See Figure 1 for recommended dosing.
    - Steroids must start 2 days before STELFONTA treatment day as directed, though patients can start steroids before this day.
    - Famotidine and diphenhydramine must be given the morning of treatment day by owners. I often start this now 2 days before treatment with the steroids.
- Consider pre-emptive pain management as STELFONTA injection results in an acute local inflammatory response followed by tumor necrosis. I recommend proactive pain management for STELFONTA patients especially the limb locations. My protocol is to have clients start gabapentin the morning of treatment @10 mg/kg PO BID and increase to TID if the dog is painful. For limb locations, be sure to advise clients about potential lameness and edema. Opioids can be added if necessary. NSAIDs must be avoided while the dogs are on steroids.

Stage 2 - STELFONTA injection:

- Important to confirm with the owner that the concomitant medication schedule has been followed.
- Accurate tumor measurement and dosing leads to better efficacy.
- Tumor Volume (cm^3) = 0.5 x [length (cm) x width (cm) x height (cm)]
- Tumor Volume should not exceed 10 cm^3
- Dose Volume (mL) = Tumor Volume(cm^3) x 0.5mL
- The formulation of STELFONTA is 1 mg per mL. The minimum dose is 0.1 mL, and the maximum dose is 0.25mL/kg body weight given in a maximum 5 mL dose regardless of tumor volume or body weight.
- While sedation is not required, it may be considered if the location of the tumor is in a sensitive location or as the patient temperament dictates.
- For safety, use a Luer-lock syringe for injection to avoid leakage and potential exposure. Always wear recommended personal protective equipment (PPE) consisting of disposable gloves, protective eye wear, and a lab coat or gown.
- A 23-guage needle is recommended.
- Disseminate the drug throughout the tumor in a fanning motion and minimize to a single injection site to prevent leakage of the drug from previous sites.
- Each vial contains 2 mL and is single use.

Stage 3 – Tumor Destruction:

- Avoid bandaging the treatment site as it may restrict blood flow or compromise healing.
- Swelling, bruising, and redness are all part of the process; wound formation is part of the mode of action and demonstrates efficacy.
- Some discharge and odor from the treatment site is expected and normal. The site can be cleaned with warm water or saline as necessary. Wear disposable gloves when cleaning the site.
- Necrotic slough is normal. If the necrotic tissue or scab is still present 14 days after the treatment, it can be removed but removal is not necessary unless the patient is not able to access the site. It is advised to NOT remove if it is adherent or attached to underlying tissue.

Stage 4 – Tumor Site Healing:

- In most patients, healthy well-developed granulation tissue is present when the necrotic tumor sloughs.
- Wounds typically heal by second intention with no intervention required. Only one patient in the clinical study had active bandage wound management.
- Elizabethan collars are usually not necessary. No restriction on activity of the dog is required. Pet can be bathed or swim with extra care taken with the treatment site.

STELFONTA Retreatment: Wait 28 days to assess response, and aspirate to confirm if there is residual MCT. I now wait until 6 weeks. If MCT is confirmed with cytology, treatment can be repeated. Concomitant medications must be repeated with the same schedule and dose.

Alternative Options for Local Disease Control: Intralesional therapies such as deionized water or corticosteroids (triamcinolone) may provide temporary shrinkage but unfortunately are rarely effective for long-term tumor control. Electrochemotherapy, cryotherapy, and photodynamic therapy are also reported. Chemotherapy including Palladia can be considered.

Supportive Medications: Any dog that has grossly detectable tumor should have supportive medications, including H1 blocker (diphenhydramine), a proton pump blocker (omeprazole) and H2 blocker (famotidine). Anti-emetics and appetite stimulants are often recommended.

Chemotherapy: Poorly differentiated and metastatic MCT will typically progress to cause morbidity, and chemotherapy is recommended. The goal of systemic adjuvant chemotherapy is to decrease the likelihood of metastasis and improve disease free intervals. Patients to be considered for chemotherapy are the high-risk patients, based on prognostic factors such as biopsy/grade, mitotic index > 5 to 7 per 10 HPF and c-kit mutation positive. Drugs used for MCT include vinblastine, Lomustine, Palladia, cyclophosphamide, hydroxyurea, and chlorambucil. Dogs with multiple MCT in a short time may also be considered for chemotherapy, as well as for non-resectable MCT in the neo-adjuvant setting (prior to surgery). Chemotherapy for non-resectable MCT is considered palliative. For dogs with measurable tumors, chemotherapy has variable response rates, and responses tend to be short-lived. Response rates of up to 64% have been reported, but studies have shown that combination therapies offer improved efficacy over single agent protocols. I prefer the combination of vinblastine and prednisone, which has reported efficacy for gross disease of 47%.

For high grade MCT and high mitotic index MCT, survival times vary due to recurrence and/or metastasis, but improved survival has been reported with aggressive local and systemic therapy, including vinblastine and prednisone, vinblastine, and prednisone with Lomustine or cyclophosphamide. Median survival times (MST) in the various studies range from 11 months to over 5 years.

A recent study showed that dogs with low-grade MCT that underwent surgical excision of the primary tumor and elective lymphadenectomy of the regional LN have a good prognosis. The use of adjuvant medical treatment in that study dogs does not seem to provide any benefit in terms of progression and survival.

How To Treat C-Kit Positive vs Negative MCT? It is important to note that dogs with both C-kit positive and negative tumors demonstrated a positive response to Palladia therapy in the pivotal clinical trial. C-kit mutation status testing is not required prior to initiation of therapy. Knowing the C-kit mutation status, however, may help guide therapy in some cases as long-term treatment with Palladia can be expensive (depending on size of dog). In cases of macroscopic, high grade, c-kit positive MCT, I will typically start with vinblastine and prednisone to reduce tumor burden more gradually prior to starting longer-term Palladia therapy. This more measured, gradual treatment approach has been better tolerated with improved overall clinical outcomes.

Steroids: Steroids can have an anti-cancer effect and decreased peritumoral edema and inflammation. As a

single agent in grade 2 and grade 3 MCT, the overall response rate (ORR) was 20% (5 of 25). But when steroids were given orally prior to radiation for non-resectable grade 1 to 3 MCT, the ORR was higher at 75% (18/24). When given prior to surgery (neo-adjuvant) for grade 1-3 MCT, the ORR was 70%.

PROGNOSIS

Mast cell tumors are treatable, but there can be a wide range of outcomes for patients. Early detection and identification with aspirates before surgery will help improve treatment outcomes. The most significant prognostic factor is tumor grade. For dogs with completely excised low-grade MCT, the prognosis is excellent. Approximately only 5% of these will recur or metastasize. For dogs with incompletely excised low and intermediate grade MCT, additional surgery or radiation is recommended. The prognosis can still be good for long term tumor control with 80-90% 2-to-5-year control rates. For high grade MCT and high mitotic index MCT, survival times vary due to recurrence and/or metastasis, but improved survival has been reported with aggressive local and systemic therapy. About 10 to 40% of dogs develop additional lesions (especially Pugs and boxers) so routine monitoring at home is so important. I recommend owners do this monthly and show them how in my YouTube video. https://youtu.be/1fHwHAUFgC8 I also recommend pet owners keep track with skin maps available on my website. https://drsuecancervet.com/pet-owner-resources/

YOUTUBE RESOURCES ON MCT & STELFONTA (feel free to share)

- 7 Things You Need to Know about Stelfonta for Mast Cell Tumors: VLOG 130 https://youtu.be/32Sq2yD_oEM
- Where'd The Tumor Go? New FDA Treatment Works For Mast Cell Tumors VLOG 131 https://youtu.be/jAb3F1g0dw0
- Stelfonta in Action for Mast Cell Tumors in Dogs Vlog 132 https://youtu.be/kNeTEd9o520
- Why I'm Excited For This New Stelfonta Mast Cell Tumor Treatment Plus More Updates: VLOG 129 https://youtu.be/7wvT1fhbJEw
- Does Your Dog Have a Mast Cell Tumor? Here's What You Need To Know VLOG 128 **https://youtu.be/9I8PGfXJ7ro**
- And Promising New Cancer Treatment for Pets Vlog 107 https://youtu.be/ybBv9Iyjvqc
- Exciting New Mast Cell Tumor Treatment for Dogs: VLOG 108https://youtu.be/HM1XgCmtJPE
- Your Dog has a Mast Cell Tumor, Now What, Part One: Vlog 63 https://youtu.be/3pmq05E8hZg
- Mast Cell Tumors in Dogs Treatment Options, Now What, Part 2 Vlog 64 https://youtu.be/IFuqwtSTR7Mo

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Figure 1: STELFONTA Concomitant medications