

DIAGNOSIS AND TREATMENT OF CANINE MAST CELL TUMORS IN 2023: LATEST ADVANCES

Sue Ettinger, DVM, DACVIM (Oncology)

Dr Sue Cancer Vet PLLC, Sleepy Hollow, NY, USA

Mast cell tumors (MCT) are the most common cutaneous tumor in dogs, accounting for 16 to 21% of skin tumors. Early detection and aspirates before surgical removal are important for successful outcomes. One size does not fit all, and MCT are treatable. While some low and intermediate grade MCT can be cured with an adequate surgery, some high grade MCT are more aggressive, with survival times of less than 3 to 6 months without treatment. Still, even dogs with high grade tumors with metastasis are treatable. Improved survival has been reported with aggressive local and systemic therapy for dogs with high grade MCT and high mitotic index.

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 the 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:

Mast cell tumors 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. 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.

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 thought that an extensive workup is not needed in most cases, unless the dog has negative prognostic factors. Buffy coats are 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** has 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 on 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 the ideal treatment in areas amenable to wide resection. The recommendations for margins have historically been 3 cm but this was largely anecdotal. More recently, surgical margins have been evaluated for MCT < 5 cm. Two cm lateral margins may be adequate for most small and lower grade (grade 1 and grade 2) MCT with 1 fascial plane deep. The majority of naïve dermal MCT are intermediate or low grade and will be cured with surgery alone, provided the site is amenable.

In some locations, such as the distal limb, wide margins are often not possible. In my opinion, amputation is probably too aggressive. For cases in which histologic margins are incomplete, further local therapy is recommended. 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.

For incomplete margins, post-operative options include scar revision (second surgery), external beam radiation therapy, chemotherapy, or monitoring. Although recurrence rates vary by study, several studies have demonstrated decreased overall survival times and/or increased local recurrence rates, so I do advise owners of these risks.

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. This provides high 2-year control rates of 85-95% 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 picosperma* (blushwood tree). It is its unique mode of action that sets it apart from other local treatment therapies. Please refer to the other session notes for more details.

Alternative Local Therapies: Intralesional therapies such as deionized water or corticosteroids may provide temporary shrinkage but unfortunately are rarely effective for long-term tumor control. Electrochemotherapy, cryotherapy, and photodynamic therapy are also reported.

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). Antiemetics 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 neoadjuvant 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 (neoadjuvant) 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>
- Promising New Cancer Treatment for Pets Vlog 107 <https://youtu.be/ybBv9lyjqc>
- Exciting New Mast Cell Tumor Treatment for Dogs: VLOG 108 <https://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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