Grading of canine mast cell tumors on a I, II, or III basis (Patnaik grade) has been the standard method for many years. This grading scheme offers some helpful information, but leaves a large percentage of tumors in the intermediate, grade II category, without readily distinguishing between the majority of grade II mast cell tumors which will go on to behave well after local control alone, and the smaller proportion of grade II tumors which ultimately metastasize.

It has been shown that mitotic index can help predict mast cell tumor behavior of grade II mast cell tumors, with patients doing better if their mast cell tumor has a mitotic index less than or equal to 5. This index is frequently available as part of the routine microscopic description on the histopathology report, and can be a useful aid in assessing the aggressiveness of a particular mast cell tumor, but is also not a perfect predictor.

More recently, a new mast cell tumor histopathology grading scheme has come into more widespread use alongside the classic Patnaik system. This promising new grading scheme divides mast cell tumors into low and high grades, in an attempt to answer the question of whether a particular mast cell tumor patient will go on to develop metastasis. Criteria for high grade tumors include at least 7 mitotic figures in 10 high powered fields, and/or the presence of substantial numbers of cells with three or more nuclei, bizarre nuclei, or karyomegaly.

All of these methods of evaluation of routine H&E sections of a histopathology sample can be helpful. But by any method, routine H&E histopathology features of a mast cell tumor can still vary at times from its ultimate behavior, and there are still some mast cell tumors, such as those with mitotic indexes close to the cutoff of 5-7, whose categorization may be equivocal.

To that end, veterinary pathologists with an interest in mast cell tumors have developed panels of additional tests which can be performed on the biopsy specimen, in an attempt to clarify the picture and better determine what a given mast cell tumor patient’s prognosis is likely to be, and whether they may benefit from adjuvant drug...
therapy. Slight variations exist among different laboratories, but commonly such panels include assessment of c-Kit pattern and c-Kit mutation status, along with various proliferative markers such as AgNOR, Ki67, and Ki67 x AgNOR index.

Ki67 is a nuclear protein which is not expressed in non-cycling cells but is expressed in cells in all phases of the cell cycle. As determined by immunohistochemical staining, the relative number of Ki67-positive cells in a tissue can thus determine the number of cells which are actively involved in the cell cycle at that moment. AgNORs, or argyrophilic nucleolar organizing regions, are substructures in the nucleolus which are involved in ribosomal RNA transcription. With silver-based histochemical staining, they can be identified microscopically as black foci within the nucleolus. AgNORs have been shown to correlate with rate of cell proliferation and tumor growth, and the AgNOR count is considered an expression of the time cells take to progress

Prognostic Evaluation of Canine Cutaneous Mast Cell Tumors

Margin Evaluation

Complete Excision

Incomplete Excision

Histologic Grading

Low Grade

High Grade

Proliferation Analysis

Low Ki67, AgNOR, Ag67

High Ki67, AgNOR, Ag67

c-Kit Analysis

PCR for c-Kit Mutation

No c-Kit Mutation

c-Kit Mutation

Evidence of RLN or Systemic Involvement

No Evidence of RLN or Systemic Involvement

Clinical Staging Evaluation of RLN, Liver, and Spleen

Evidence of RLN or Systemic Involvement

No Evidence of RLN or Systemic Involvement

Eating Local Evaluation

Complete Excision

Incomplete Excision

Wide Local Excision Possible

Wide Local Excision Not Possible

No Additional Therapy

Wider Excision or Local Radiation Therapy

Radiation Therapy

Systemic Chemotherapy

Candidate for Tyrosine Kinase Inhibitor Therapy

Candidate for Tyrosine Kinase Inhibitor Therapy

Not a Candidate for Tyrosine Kinase Inhibitor Therapy

Systemic Chemotherapy

No Additional Therapy

Systemic Chemotherapy

Candidate for Tyrosine Kinase Inhibitor Therapy

No Additional Therapy

An example of a flowchart for possible therapeutic decisions regarding mast cell tumors, based on results of staging tests and evaluation of the histopathology sample (including microscopic features, proliferative markers, c-Kit testing, and margin evaluation).

Chart courtesy of Michigan State University Diagnostic Center for Population and Animal Health, reprinted with permission. See www.animalhealth.msu.edu for more information.

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through the cell cycle. In combination, therefore, Ki67 (representing the number of cycling cells) and AgNORs (demonstrating generation time for the cell cycle) provide a better measurement of the cellular proliferation rate than mitotic index, or than either value alone. A Ki67 count of >23 has been shown to be associated with decreased prognosis for mast cell tumor patients (increased local recurrence, increased development of mast cell tumor elsewhere, and increased mast cell tumor-related mortality). A Ki67 x AgNOR value of >54 was similarly associated with worsened prognosis in the same study.

C-Kit is commonly evaluated in two ways. One method is c-Kit staining pattern as determined by immunohistochemistry; three different staining patterns are recognized. Kit pattern I, the pattern seen in normal, non-neoplastic mast cells, consists of primarily peri-membrane Kit protein localization. Kit pattern II shows focal to stippled cytoplasmic Kit protein localization, and Kit pattern III shows diffuse cytoplasmic Kit protein localization; both these patterns of intracytoplasmic KIT staining have been associated with a poorer prognosis.

The specific numbers vary with the study population, but a substantial percentage of mast cell tumors possess activating mutations in the c-Kit gene, most commonly in exon 11, with less common mutations in other gene regions. Constitutively activated c-Kit can result in neoplastic mast cell proliferation in the absence of appropriate external signals to divide. C-Kit is a receptor tyrosine kinase and thus a target of tyrosine kinase inhibitors drugs such as toceranib phosphate (Palladia®) and masitinib (Kinavet®). Drugs such as Palladia have been shown to induce responses in mast cell tumors with and without activating c-Kit mutations, but response rates are higher in tumors with the c-Kit mutation than in those without (69% versus 37% response rates in one Palladia study).

The perfect decision tree for mast cell tumor treatment is still a work in progress. But, more and more, oncologists are using results of these mast cell tumor panels to assist in decisions regarding when and how to treat equivocal mast cell tumors. If proliferative panels suggest aggressive behavior, adjuvant drug therapy is generally recommended to try to prevent or delay metastasis. Classically, this has meant treatment with chemotherapy drugs such as vinblastine or CCNU, often in combination with prednisone. Now, with newer tyrosine kinase inhibitors available, these TKIs could potentially be used instead of or in addition to chemotherapy. In many but not all cases where both chemotherapy and TKIs are used in a patient’s treatment, they are used sequentially rather than simultaneously, due to the risk of toxicity when used in combination.

While there is much we are still learning about optimal treatment of mast cell tumors with different features, these newer tests offer improved insight into which mast cell tumors will require adjuvant therapy of one type or another. Assessment of c-Kit pattern and mutation status may also give a rationale for treatment choice; some oncologists are starting to choose tyrosine kinase inhibitors as initial treatment if there is a mutation in c-Kit and chemotherapy as first line treatment if no c-Kit mutation is present, though further studies are needed to determine if this is the optimal approach.

References:


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EXCELLENCE
At Arizona Veterinary Specialists, our standard is excellence in all that we do and the way in which we do it.

COMPASSION
The spirit of all our relationships will be driven by compassion.

PATIENT CARE
We are committed to providing compassionate, ethical, and quality care to our patients. We treat them as if they are members of our own families.

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♦ Glaucoma treatment
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♦ Treatment of eyelid abnormalities

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♦ Linear accelerator radiation therapy
♦ I-131 radioactive iodine treatment

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♦ Bacterial and fungal skin disease diagnosis and treatment
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♦ Ectoparasite identification and treatment
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♦ Skin biopsy sampling and histopathology interpretation

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♦ Outpatient and inpatient ultrasound
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♦ Radiographic interpretation
♦ CT and MRI interpretation

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Emergency Animal Clinic, PLC

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    ♦ Radiologist interpretation
  • Scanning ultrasound
  • Gastrointestinal endoscopy
♦ Specialized Therapies
  • Intravascular volume expansion/shock therapy
  • Blood component therapy
  • Rattlesnake antivenom therapy
  • Oxygen
  • Short and long term ventilator therapy
  • Anesthetic ventilator
  • Pain medication delivery via constant rate infusion
  • Nutritional support
  • Feeding tube placement
  • Peritoneal dialysis
  • Continuous suction for chest and other drains
  • Central and peripheral IV catheter placement
  • CPR with advanced life support
  • Electrical defibrillation & emergency cardioversion
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♦ Soft tissue emergency surgical procedures performed by our emergency veterinarians (included, but not limited to):
  • Wound repair
  • Emergency tracheostomy
  • Chest tube placement
  • Abdominal surgeries
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  • GI foreign body removal
  • C-section
  • Splenectomy
  • Bladder stone removal
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