What’s New in Mast Cell Tumors

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Pathology Reports

What are we discussing today?

- Many faces of MCT
- Staging: How much is too much?
- Grading: I,II,III vs. High grade, Low grade
- Biopsy margins: am I ok with 5mm?
- MCT panels: when are they needed?
- Let’s eat!

Many faces of MCTs
Diagnosis
- Usually easily diagnosed cytologically
- Grading requires histologic evaluation

MCT & Bone Marrow
- What % of dogs with a first and second (respectively) Grd II MCT will be bone marrow POSITIVE?
  - A 0% & 2%
  - B ~ 1% & 2%
  - C ~ 1% & 8%
  - D 10% & 18%
  - E 10% & 29%

MCT & Bone Marrow
- Degree of Staging is Controversial
  - Full Physical exam, bloodwork and UA
  - Abdominal ultrasound?
    - VERY CONTROVERSIAL
      - Studies suggesting NOT helpful for predicting spread
        - Book et al. Vet Radiol Ultras 2011 – Approx half = mets but no AUS changes
      - Studies suggesting it is HELPFUL
        - Sato et al. Vet Radiol Ultras 2004
        - Finora et al. JVIM 2006
        - Stefanello et al. JVIM 2009
    - MY APPROACH: No ultrasound unless to follow with radiation therapy or clinically ill
Lymph node evaluation:
- Krick et al. VCO 2009
  - LN+ MST = 0.8 years vs LN- = 6.2 yrs
  - Grd III more likely to be LN+
- Weishaar et al. J Comp Pathol 2014
  - New histologic classification system
    - Number and distribution of nodal mast cells
    - Architectural disruption by nodal mast cells
    - Severity was associated with decreased DFI and survival
- I always recommend excision of draining LN

Bone marrow aspiration & cytology?
- Enicott et al. Vet Comp Oncol, 2006
- Marconato et al. JVIM 2008
  - BM + = 43d MST
- Questionable use in cats with solitary dermal/SQ lesion
- Diagnostics of no benefit in dogs??
  - Buffy Coat
    - May be of use in cat MCT staging!
  - Garrett et al. JAVMA 2007
  - Skeldon et al. JFMS 2010
  - Thoracic radiography?
    - How could chest films be helpful with MCT staging??

WHO Staging scheme
- Stage I
  - Single skin tumor, LN –
- Stage II
  - Single skin tumor, LN +
- Stage III
  - Multiple skin tumors
- Stage IV
  - Any tumor, distant metastasis
- Problems with staging scheme??
  - Multiple skin tumors worse than LN+?
- Murphy et al. Vet Rec Mar 2006
  - No difference between stage I vs III
  - Stage II did worse than III
- Mullins et al. JAVMA Jan 2006
  - 54 dogs with stage III disease, DFI > 5 yrs
  - Clinical signs = multivariate prognostic
  - Suggestive of metastasis?
- O’Connell A, Thomson, VCO 2011
  - Bad Px if one or more is Grade III or High grade
  - Better Px if < 3cm, MI < 5 & limb location
  - SWOTCh Stages II/III

FNA Regional LNs
Abdominal Ultrasound:
  - Only if:
    - Clinical signs
    - Radiation therapy to follow
Thoracic Radiographs
  - General health of patient
  - If MCT in cranial ½ of body

Mast cell tumor Grading
- Grade I: Well Differentiated
  - I (36%)-well diff (10%)
  - Cytoplasmic boundaries
  - Nuclear shape/size
  - Mitotic index
  - Granules
  - II (43%)-mod. diff (80%)
  - III (20%)-poorly diff./anaplastic (10%)

Staging Summary: What do I do?

MCT Grading
- Grade II: Moderately-Differentiated
- Grade III: Poorly-Differentiated
  - w/ infiltrative growth
MCT: Grading issues

- SUBJECTIVE!!
- Northrup et al. J Vet Diagnostic Invest 2005
  - 60 MCT (20/grade)
  - 10 pathologists (blinded)
    - 4/60: all 10 agreed
    - 6/60: assigned all 3 grades

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<th>Disagree</th>
<th>Total</th>
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<td>227</td>
<td>616</td>
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<td>3</td>
<td>188</td>
<td>64</td>
<td>252</td>
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<tr>
<td>Total</td>
<td>1706</td>
<td>954</td>
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Grade 3: 74.6%
Grade 2: 63.0%
Grade 1: 63.1%
POOR!!!

Histologic Grading Concordance and Proposal of a 2-Tier Histologic Grading System

Proposal of a 2-Tier Histologic Grading System for Canine Cutaneous Mast Cell Tumors to More Accurately Predict Biological Behavior


New 2-tier Grading Scheme

- 2-tier system proposed, “High” vs. “Low”
  - Criteria for “high”:
    - MI > 7
    - 3+ multinucleated cells
    - 3+ bizarre nuclei/ 10 hpf
    - karyomegaly
  - Survival:
    - High grade < 4 months
    - Low grade > 2 years

MCTs: Therapy

- Therapy
  - Know what you are treating before you treat it
  - Cytology prior to surgery
  - Most important for distal limb lesions (“one chance”)
  - Surgery, surgery, surgery!!
    - “3 cm rule”
      - 3 cm margins laterally
      - 3 cm margins deep OR 1 fascial plane deep
    - CONTROVERSIAL: 3 cm rule under investigation @ many sites
    - En toto removal (all layers removed in continuity)
**Mast Cell Tumors: Magic 3 cm Rule??**

- Simpson et al. JAVMA '03
  - 23 dogs with grade II MCT and clean staging
  - 3 cm lateral margins and 1 fascial plane deep
  - Systematic margin evaluation q 1 cm laterally
    - 1 cm = 75% clean; 2 cm = all clean

- Fulcher et al. JAVMA 2006
  - all clean with 2 cm margins !!

- Pratschke et al, JAVMA 2013
  - Proportional Margins study (diameter = lateral margin)
  - 85% clean margins vs 15% incomplete margins

**Suggests:**
- 2 cm lateral margins may be appropriate for most grade II MCT
- How often do we know grade pre-op though??

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**Mast Cell Tumors: Margins?**

- What is a TRUSTABLE clean margin length for MCT from YOUR histopath report?
  - Schultheiss et al. JAVMA June 2011
    - 115 Patnaik Grd I or II MCT’s with various length margins
    - Followed for minimum of 27 months
    - Margins that = no recurrence:
      - Lateral = 10 mm & Deep = 4 mm
    - NOTE:
      - Less than this length may still not recur
      - Equal to or longer should NOT recur

- Does this depend on the grade? YES!!
  - Donnelly et al. VCO 2013
    - High risk of recurrence for high grade tumors independent of margin length
    - Low risk of recurrence in low grade tumors in face of < 3mm margins

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**Mast Cell Tumors & Sx**

- What percent of dogs with a grade II MCT surgically removed with clean margins will develop local tumor recurrence?
  - A  0%
  - B  1-2%
  - C  5-10%
  - D  15-20%
  - E  > 25%

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**Mast Cell Tumors and Surgery**

- Surgery
  - 1st sx often curative
  - 2nd sx for incomplete resection
    - Grade II, complete excision
    - Recurrence = 30%
    - Distant 22%
    - 18.5 months
    - Local 10%
    - 21 months
    - MST = 791d

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**Mast Cell Tumors & Sx**

- What % of dogs with Grade II MCT treated with Sx and incomplete margins will have local tumor recurrence?
  - A  100%
  - B  86-99%
  - C  66-85%
  - D  17-38%
  - E  < 15%
**Mast Cell Tumors & Sx**

- What % of dogs with Grade II MCT treated with Sx and incomplete margins will have local tumor recurrence?
  - A 100%
  - B 86-99%
  - C 66-85%
  - D 17-38%
  - E < 15%

**MCT: What do I recommend?**

- Most aggressive surgery possible
- High probability of clean margins
- Difficult region—→neoadjuvant prednisone
- Low grade and margins >3mm—no further tx
- High grade >5mm needed
  - Second surgery
  - Radiation therapy
  - Chemotherapy
  - TKI?

**MCT Panels: Proliferation Indices**

- AgNOR
- PCNA
- Ki-67

**MCT-Surgery**

- Neoadjuvant prednisone
  - 1-2.2mg/kg po sid
  - 70% RR
    - Max Diameter reduction=45.2%
    - Tumor volume reduction=80%
  - No diff in pred dose
  - Makes sx easier
    - Margin analysis?

*Stanclift et al. JAVMA 2008*

**Mast Cell Tumors**

- What is the recurrence rate with dirty margins?
  - Dirty little secret in oncology!
  - 17%–38% recurrence rate across SIX Studies
  - Local recurrence = ~ 60% progression of malignancy
    - Abusle et al. JVMA 1999
  - Is additional Rx necessary for ALL incompletely resected MCT?
    - YES, for now; either re-resection or radiation therapy
    - Decreases local recurrence & increases survival (Kry & Boston, Vet Surg 2014)
  - Prognosticating recurrence would be VERY beneficial
    - Directs prognosis & treatment decisions
    - KS2 A PCNA combination predicted which recurred locally (Seguin et al. JVIM 2006)
  - What is a dirty margin?? Differs across pathologists & oncologists!!

**Mast Cell Tumors: Mitotic index**

- Quick and dirty method
- <5/10 HPF = MST > 70 months
- >5/10 HPF = MST < 2 months
- Grade II: “Garden Variety” vs. aggressive

*Romansik et al. 2007*
**MCT panels: Understanding Kit**
- **IHC (CD117)**
- c-kit proto-oncogene
- Gene product = Stem cell factor receptor (CD117)
- c-kit is a transmembrane tyrosine kinase receptor

*Krupel et al. Vet Path 2004*

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**MCT Panels: KIT staining**
- I: perimembrane protein localization
- II: focal to stippled cytoplasmic staining
- III: diffuse cytoplasmic staining = Poor prognosis

*Webster et al. Neoplasia 2006*

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**MCT Panels: Kit mutation**
- c-kit ITD assay to determine if MCT contains an exon 8, 11 activating mutation
- Cytology or histopathology samples
- Mutation + has a poor prognosis

*Kiupel et al. Vet Path 2004*

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**MCT Panels: When?**
- † MCT panel delineates † risk of developing metastasis
  - Suggests need for adjuvant chemotherapy – efficacy studies ongoing
- † MCT panel delineates † risk of local recurrence
  - Suggests need for additional local therapy
  - Tougher call when have > 1 cm margins
  - BEST SCENARIO = GUIDES Rx decisions with incomplete resection
- Berlato et al. VCO 2013
  - Head to head comparison of MI and Ki67 (n = 95 dogs)
  - Ki67 alone was better than MI

*MCT panels sites:
- Antech can send to MSU for full panel or CSU (but no AgNOR)
- AMC/IDEXX
- Michigan State – Dr. Matti Kuipel

*Berlato et al. VCO 2013*

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**MCT Panels: What do I do?**
- All High grade/Grade III → Kit mutation testing
  - Positive: Chemotherapy + TKI
  - Negative: Chemotherapy alone
- When run a full panel?
  - Grade II: but increased mitotic index >5
  - Biologic behavior does not fit histopathology
    - Tumor growing rapidly, large, etc
  - "hot site": muzzle, mucocutaneous
MCTs: Summary

- Many faces of MCT:
  - Always aspirate a lump!!
- Degree of staging highly controversial
  - Oncologist dependent
- Grading: Moving to a 2-tier system
  - 5% low grade behave "against the grain"
- MCT panel: Not for every case!

Questions?

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