


vca


Updates on Surgical Management of Canine Mast Cell Tumors

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Mast Cell Tumors – Overview

- MC dermal tumor in dogs; 2nd MC in cats
 - 16-21% cutaneous tumors dogs
- Middle-age to older dogs (8-10 years)
 - English bulldogs, boxer, Boston terrier, Pugs, Labs, retriever, Goldens, Cocker spaniel, Schnauzer, Beagle, Rhodesian ridgeback, Weimaraner, Shar pei
- Dogs of bulldog descent are typically less aggressive
 - Anecdotal evidence that Shar pei have higher grade tumors
 - Polymorphism in GNAI2 and other genes responsible for hyaluronic acid increased risk in Goldens (*Arendt et al, Plos Genit, 2015*)




Overview

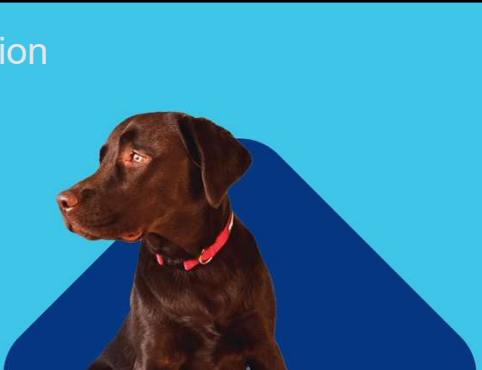
- Introduction
- Diagnostics/Staging
 - FNA
 - Advanced imaging
 - LN Mapping
 - Cytological grading
- Surgical Dose
- Surgical Principles
- Conclusions

Mast Cell Tumors – Overview

- Can occur anywhere
 - Trunk or perineal region – 50%
 - Limbs – 40%
 - Head/neck – 10%
- 14% of dogs will have multiple tumors on presentation
- Conjunctiva, salivary gland, oral/buccal mucosa, nasopharynx, larynx, ureter, spine, anal sacs also reported
 - Primary intestinal MCT



Introduction



Mast Cell Tumor – Overview

- The tumor location can be prognostic
 - Subcutaneous tumors more favorable
 - Mucosal, subungual, oral, genital, anal/perianal
 - Visceral and bone marrow have a poor prognosis



Factor	Comment
Histologic grade	Strongly predictive of outcome. Dogs with undifferentiated tumors typically die of their disease after local therapy alone, whereas those with well-differentiated tumors are usually cured with appropriate local therapy.
Clinical stage	Stages 0 and 1, confined to the skin without local lymph node or distant metastasis, have a better prognosis than higher-stage disease.
Location	Subungual, oral, and other mucous membrane sites are associated with more high-grade tumors and worse prognosis. Preputial and scrotal tumors are also associated with a worse prognosis. Subcutaneous tumors have a better prognosis. Visceral or bone marrow disease usually carries a grave prognosis.
Cell proliferation rate	Mitotic index, relative frequency of AgNORs, and percent PCNA or Ki-67 immunopositivity are predictive of postsurgical outcome.
Growth rate	MCTs that remain localized and are present for prolonged periods of time (months or years) without significant change are usually benign.
Microvessel density	Increased microvessel density is associated with higher grade, a higher degree of invasiveness, and a worse prognosis.
Recurrence	Local recurrence after surgical excision may carry a more guarded prognosis.
Systemic signs	The presence of systemic illness (e.g., hyporexia, vomiting, melena, GI ulceration) may be associated with a higher stage of disease.
Age	Older dogs may have shorter median disease-free intervals when treated with radiation therapy than younger dogs.
Breed	MCTs in boxers (and potentially other brachycephalic breeds) tend to be of low or intermediate grade and are thus associated with a better prognosis.
Sex	Male dogs had a shorter survival time than female dogs when treated with chemotherapy.
Tumor size	Large tumors may be associated with a worse prognosis after surgical removal and/or radiation therapy.
c-kit mutation	The presence of an activating mutation in the c-kit gene is associated with a worse prognosis.
DNA copy number variation	Higher CNs are observed in tumors of higher grade and those with a worse prognosis.

AgNORs, Argaphic nuclear organizer regions; CN, copy number variation; GI, gastrointestinal; MCT, mast cell tumor; PCNA, proliferating cell nuclear antigen.

Withrow, Small Animal Onco, 2020

Diagnostic Approach to Cancer

- Complete bloodwork
- Fine-needle aspirate
- Thoracic radiographs
- Advanced imaging
 - Ultrasound
 - CT scan
- +/- Liver and splenic aspirates
- Sentinel LN mapping



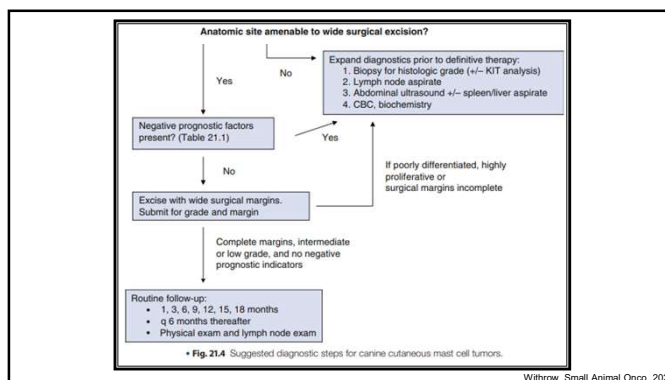

Photo Credit: Dr. Andrea Erickson

Mast Cell Tumor – Overview

- Variable appearance
 - Fluctuation in size
 - Alopecic
 - Ulcerated
 - Darier Sign
- Systemic clinical signs
 - GI signs – Vomiting, diarrhea
 - Peripheral edema
 - Bruising
 - Collapse



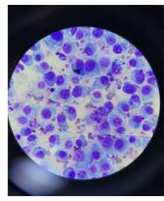
Withrow, Small Animal Onco, 2020

Diagnostics and Staging

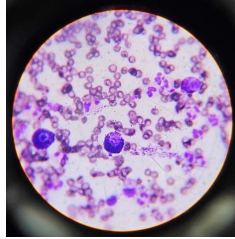
Diagnostics: FNA

- Great initial, non-invasive diagnostic tool
 - Can be diagnostics for many tumors
 - MCT, melanoma, lymphoma, etc
- Sensitivity of cytologic examination ranges from 33.3 to 61.6% (Cohen et al, JAVMA, 2003)
 - Cytology is most accurate for cutaneous and SQ lesions
- Evaluation of FNA as a diagnostic for skin and SQ lesions (Ghisleni et al, Vet Clin Pathol, 2006)
 - Cytology agreed with histopath 90.9% of cases
 - High sensitivity (89.3%) and specificity (97.9%) in diagnosing neoplasia



Diagnostics: FNA

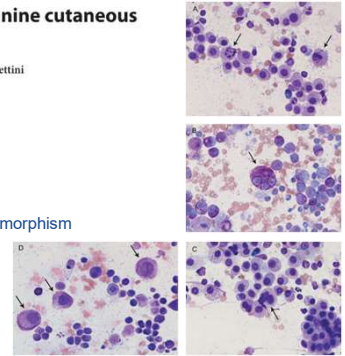
- Cytology can also be used to evaluate for metastasis
- FNA has a sensitivity of 66.6% for diagnosing neoplasia (*Ku et al, Vet Comp Oncol, 2016*)
 - Specificity 90.1%
 - Accuracy 77.2%
 - Higher proportions of false negatives with
 - Mesenteric T-cell lymphoma (63%)
 - Metastatic sarcomas (57%)
 - Metastatic MCT (31%)



Cytological grading of canine cutaneous mast cell tumours

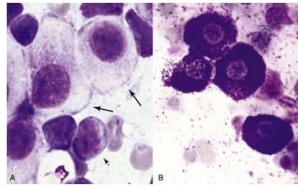
Filippo Scarpa, Silvia Sabbatini and Giuliano Bettini

- 50 cases cutaneous MCT
- For each case 1000 mast cells morphologically evaluated
- Area of high cellularity and pleomorphism
 - Mitoses
 - Multinucleated cells
 - Bizarre nuclei
 - Karyomegaly



Diagnostics: Cytology

- Heterogenous population of small to medium size round cells
 - Eosinophils, fibroblasts, lymphocytes
- Metachromatic staining cytoplasmic granules
 - Occasionally granules don't stain readily and give the cells a "fried egg" appearance
 - Wright-Giemsa
 - Toluidine blue stain
- Anaplastic MCT are more difficult to assess cytologically

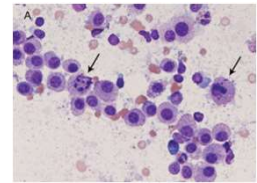


Withrow, Small Animal Onco, 2020

Cytological grading of canine cutaneous mast cell tumours

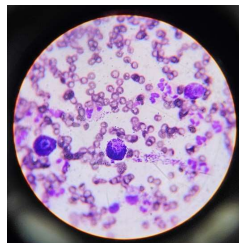
Filippo Scarpa, Silvia Sabbatini and Giuliano Bettini

- 74% low-grade
- 26% high-grade
 - Number of mitoses, multinucleated cells, bizarre nuclei, and karyomegaly statistically higher in high-grade tumors
- Histologic grade correctly predicted in 94% cases



Diagnostics: Cytologic Grading

- Different criteria have been used to try and predict the behavior of MCT
 - Clinical stage, c-kit mutations, proliferative activity, etc
- Histopathologic grade is most reliable
- Multiple studies have evaluated a grading scale for FNA cytology

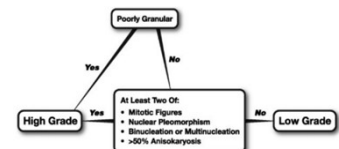


Diagnostics: Cytologic Grading

- *Camus et al, Vet Path, 2016*
– Cytologic Criteria for MCT Grading

- 2-tier histologic grading scheme for MCT to predict outcome

- 152 MCT
- Based on karyomegaly, multinucleation, nuclear pleomorphism, mitotic figures



Cytologic Criteria for Mast Cell Tumor Grading in Dogs With Evaluation of Clinical Outcome

M. S. Camus¹, H. L. Priest², J. W. Koehler³, E. A. Driskell⁴, P. M. Rakich⁵, M. R. Ilha⁶, and P. M. Krimer³

- Histopathologic grade
 - 88.8% low-grade, 11.2% high-grade
- Cytologic characteristics associated with 2y survival
 - Granularity, Anisokaryosis, Multinucleated cells, Binucleated cells, Mitotic figures
 - Bizarre nuclei, nuclear pleomorphism, collagen fibrils had
- High-grade cytology
 - Poorly granular
 - 2 of the following features:
 - Presence of mitotic figures
 - >50% Anisokaryosis
 - Binucleation or multinucleation
 - Nuclear pleomorphism
- 88% sensitivity; 94% specificity

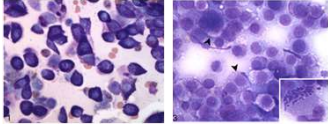
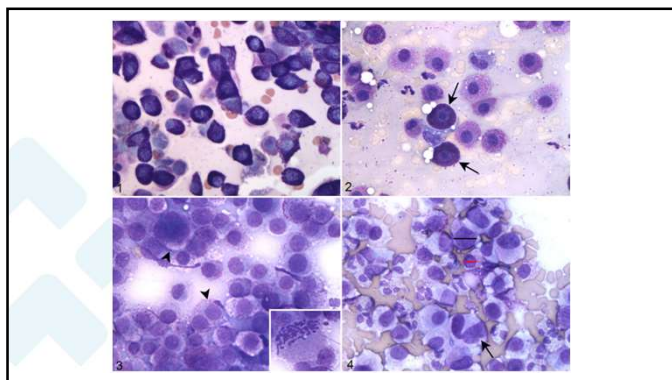


TABLE 1 Criteria applied for cytologic grading canine mast cell tumors

Variable (magnification)	Criterion
Cellularity (40 and/or 100x)	High: cells cover 1/3 of the slide Intermediate Low (approximately 100-200 cells per slide)
Proportion of clustered cells (40 and/or 100x)	≥40%
Concentration of fibroblasts and/or collagen fibrils (100x and 400x)	Intermediate to high (moderate to intense concentration in at least some areas of the slide)
Concentration of eosinophils and/or neutrophils (100x and 400x)	Low/absent
Cytoplasmic granulation of mast cells (100x and 400x)	Intermediate to high (moderate to intense concentration in at least some areas of the slide) High Poor (scarce to absent)
Binucleated and multinucleated mast cells, anisocytosis, mitotic figures, karyomegaly (100x and 400x)	Present Absent


Note: Cytologic high-grade mast cell tumors presented poor granulation or, in the presence of high cytoplasmic granulation, at least two of the following four criteria: presence of multinucleated cells, mitotic figures, karyomegaly, and low/absent concentration of fibroblasts and/or collagen fibrils.

Paes et al. Vet Clin Pathol, 2022



Diagnostics: Thoracic Radiographs

- Low cost, available in most practices
 - Good screening tool
- Orthogonal views!!
 - Position dependent atelectasis can reduce lesion identification
 - 12-15% diagnosis would change with 2 views
- Thoracic radiographs are lower-yield diagnostic for MCT

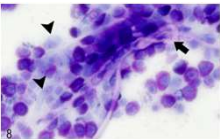


<https://twitter.com/drmunster/status/99097515998256774>

Inclusion of fibroblasts and collagen fibrils in the cytologic grading of canine cutaneous mast cell tumors

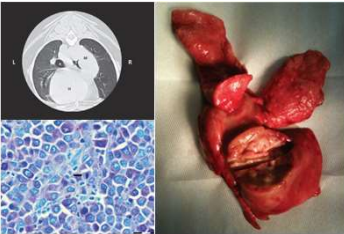
Paulo R. O. Paes¹ | Rodrigo S. Horta² | Ludimila C. Luza³ | Felipe Pierezan⁴ | Mariana P. Costa⁵ | Gleidice E. Lavalle⁶

- Proposed a grading scheme based on MCT microenvironment
 - Associated with mortality and histologic grade
- 92 first-occurrence MCT → 5 cytologic features
 - Cytoplasmic granulation
 - Fibroblast and/or collagen fibril concentration
 - Presence of mitotic figures
 - Multinucleation
 - Karyomegaly
- Higher concentrations fibroblasts and/or collagen fibrils were associated with increased survival and lower histologic grade



Diagnostics: Thoracic Imaging

- Campbell et al. *Can Vet J*, 2017 - Presumptive primary pulmonary MCT in 2 dogs
 - 6yo FS American Bulldog
 - 11yo FS Mixed breed poodle
 - Both euthanized
 - Systemic signs of hyperhistaminemia
 - No primary tumor



Diagnostics: Abdominal Ultrasound

- Distant metastasis is often to the liver and the spleen
- Abdominal ultrasound is recommended for patients with negative prognostic factors
 - Multiple previous MCT
- Splenic and liver aspirates are controversial
 - **Rinaldi et al, Vet Sci, 2022** – 1/136 dogs had presence of visceral metastasis in dogs with low grade MCT
 - Recommend with negative prognostic factors, evidence of LN metastasis, high grade tumors
 - For owners who would like a complete work-up prior to surgical decision

Diagnostics: Sentinel LN Mapping

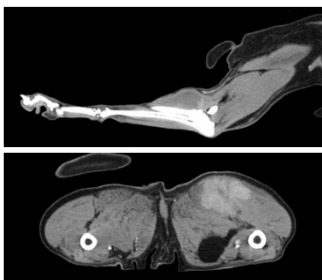
- The sentinel LN is the first LN to which cancer is likely to spread
 - Regional LN may not be representative
 - Standard of care in human medicine since the 1990's
- Involves the injection of a radioactive marker around the tumor followed by scintigraphy
 - Visual identification with methylene blue and the use of a gamma probe intra-op is also commonplace
- Indirect lymphangiography is an alternative
 - Peritumoral injection of contrast agent followed by imaging
 - Contrast enhancement of LN



Collivignorelli, Animals, 2021

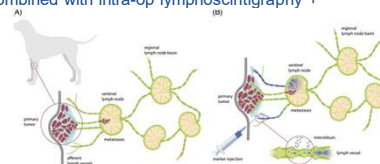
Diagnostics: Advanced Imaging

- CT or MRI can be used for surgical planning
 - Tumors well margined on MRI → rarely used
 - Use of CT for planning has limitations including location, poor contrast enhancement, delineation between normal and abnormal (**Farmer et al, Vet Radiol Ultrasound, 2023**)



Diagnostics: Sentinel LN Mapping

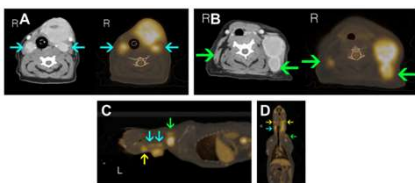
- **Worley, Vet Comp Oncol, 2014** – SLN mapping in 20 dogs with cutaneous MCT
 - Regional lymphoscintigraphy combined with intra-op lymphoscintigraphy + methylene blue
 - 8/20 dogs have SLN different from closest node



Beer, Vet Comp Oncol, 2017

Diagnostics: Advanced Imaging

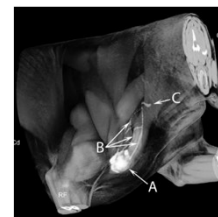
- PET/CT has been evaluated for full-body staging
 - Correlation between standard update max and histologic grade using ¹⁸FDG PET/CT (**Griffin et al Vet Radiol Ultrasound, 2018**)



Influence of locoregional lymph node aspiration cytology vs sentinel lymph node mapping and biopsy on disease stage assignment in dogs with integumentary mast cell tumors

Jarvis Lapsley DVM, Galina M. Hayes BVSc, DVSc, PhD, Valentin Janvier DVM, Ashleigh W. Newman VMD, Jeanine Peters-Kennedy DVM, Cheryl Balkman DVM, Julia P. Sumner BVSc, Philippa Johnson MSc


- 17 dogs underwent primary excision of 20 cutaneous and SQ MCT
 - FNA of the locoregional LN was compared to the histopath of SLN
 - SLN differed from the locoregional LN in 5/18 scans
 - Mets detected in 9/20 SLN compared to 1/20 FNA locoregional LN



- SLN consistently identified with indirect CT lymphangiography and differed from locoregional LN in 25%

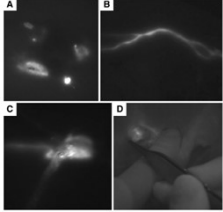
Diagnosics: Sentinel LN Mapping

- **Annoni et al, Vet Comp Oncol, 2023** - Use of radiographic indirect lymphography
 - 136 cytologically diagnosed MCT
 - Serial radiographs after peritumoral injection iomeprole at 1, 3, 6, 9min
 - 168 sentinel LN identified at first radiograph
 - Remainder at 3min
 - Sentinel LN differed from regional LN in 57% cases
 - Multiple SLN identified in 26% cases



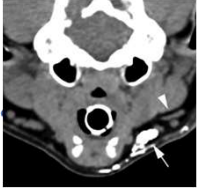
Diagnosics: Sentinel LN Mapping

- Near-Infrared (NIR) fluorescent image-guided lymph node dissection compared with locoregional lymphadenectomy (**Beer et al, JSAP, 2022**)
 - MCT excision with either NIR fluorescent lymphadenectomy and without NIR
 - 35 patients with 43 LN
 - 83% ID with NIR vs 74% without NIR
 - NIR fluorescence imaging led to ID of additional LN in 15/35
 - NIR allowed for ID of at least one metastatic LN in 60% compared to 20% without imaging




Diagnosics: Sentinel LN Mapping

- **Ferraris et al, Vet Comp Oncol, 2023** – feasibility study evaluating CT lymphography in veterinary patients
 - 62 MCT
 - Detection rate of 90%
 - Failure to ID in 6 patients
 - SLN did not correspond with regional LN in 32%
 - In 45 cases, both sentinel and regional LN removed
 - Stage of disease would have changed in 7%
 - If the SLN removed, not other LN need to be removed

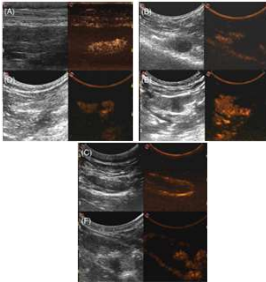


Surgical Dose



Diagnosics: Sentinel LN Mapping

- **Fournier et al, Vet Comp Oncol, 2021** – Evaluate the use of contrast-enhanced ultrasound in the ID of SNL
 - 59 dogs with 62 MCT
 - Contrast-enhanced US ID at least one SLN in 59/62 MCT (95.2%)
 - Clinician evaluation would have only predicted SNL in 32-59 (54.2%)
 - 60% SNLN had evidence of metastasis



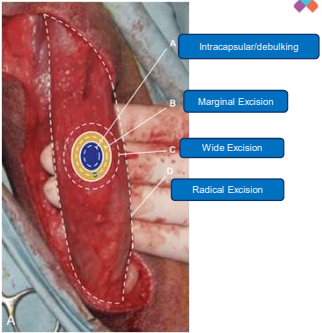
Surgical Dose: Developing a Tx Plan

- Tumor type and grade (if known)
- Extent of disease
- Evidence of mets or potential for metastasis
- Comorbidities
- Prognostic factors
- Owner finances
- Owner expectation
 - And compliance!!
- Curative intent?
 - Non-surgical options
 - Chemo
 - RT
 - Electrochemo
 - Functional cost to patient
 - Cosmetic cost to owner



Surgical Dose

- The best opportunity to cure is with the initial surgery
 - Increased risk for recurrence, spread, or delayed adjunctive therapy with multiple surgeries
 - Abnormal scar tissue
 - Changes in vascularity



Withrow, Small Animal Clinical Oncology, 6th Ed


Surgical Dose: Marginal Excision

- Cockburn et al, JAVMA, 2022** – No difference in healing compared with marginal excision STS
 - 29% vs 31%
 - Subdermal plexus flap associated with complications and increased healing time
- Potential to follow with adjunctive electrochemotherapy or RT




Surgical Dose: Debulking

- The worst.
 - Leave behind gross disease
 - Subtotal removal potentially selects for the most aggressive cells peripherally
 - Healing complications with gross residual disease
 - Potential to follow with adjunctive radiation therapy



Surgical Dose: Marginal Excision

- Planned narrow excision
 - Remove as much disease as possible to maintain function
 - Residual ("R") tumor scheme
 - R1 incomplete; R0 complete margins
- Haine et al, Vet Surg, 2022** – Evaluation of planned narrow margins in appendicular STS and MCT
 - 0-5mm margins resulted in R1 margins 55% whereas 6-10mm margins resulted in R1 7% for MCT
 - Recurrence rate 11%



Surgical Dose: Marginal Excision

- Removal of all macroscopic disease
 - Remnant microscopic disease
- Aggressive surgical excision may not be recommended based on:
 - Age
 - Comorbidities
 - Owner goals



Withrow, Small Animal Clinical Oncology, 6th Ed

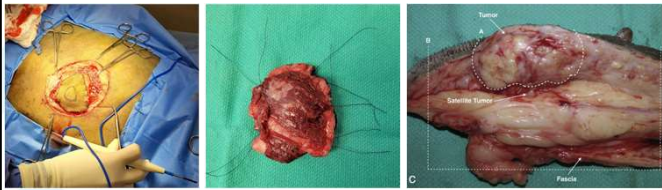
Surgical Dose: Wide Excision

- Curative Intent
- Identify intended surgical margins
- Advanced imaging may be useful
- Understand lines of tension
- Primary closure vs advanced reconstruction
- Delayed closure?
- Drain placement?



Photo Credit: Dr. Andrea Erickson

Surgical Dose: Surgical Margins



Tobias and Johnston: Vet Surgery, 2017



Surgical Dose: Surgical Margins

- Mast Cell Tumor (dog) - generally 2-3cm lateral margins and 1 fascial plane deep
 - Low grade MCT, <4cm in size → 2cm lateral margins and 1 fascial plane deep (*Selmic, BMC Vet Res, 2020*)
 - *Pratschke, JAVMA, 2013* → modified proportions surgical approach
 - 40/47 completely excised; Local recurrence suspected in 1 dog not confirmed
 - *Saunders, Vet Comp Oncol, 2021* → 95% MCT completely excised
 - 2cm is the upper limit
 - Upper limit for proportional margins excision of MCT
 - Recurrence rate 3%

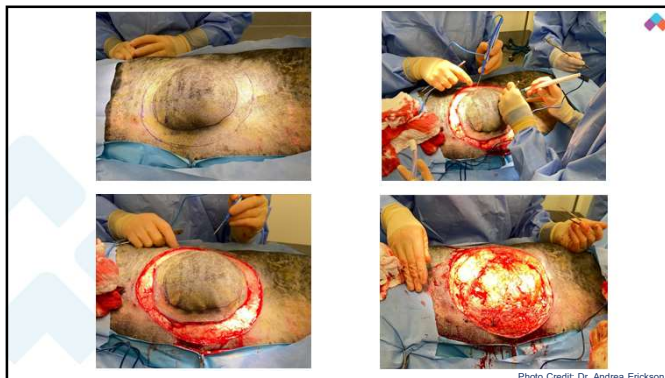
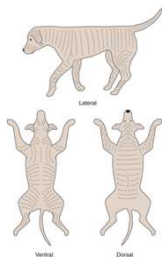


Photo Credit: Dr. Andrea Erickson

Surgical Dose: Wide Excision

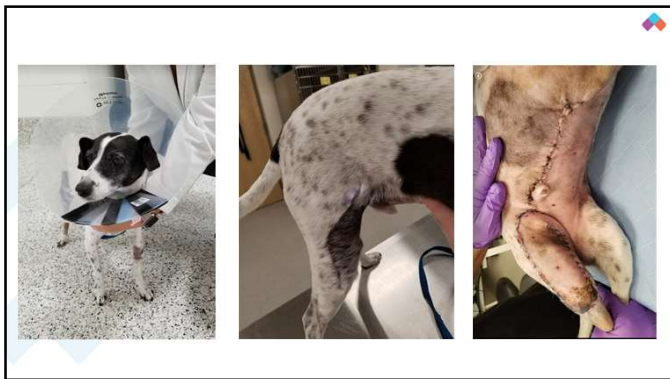
- Understand lines of tension
 - Skin-stretching may be useful for large masses
 - Mechanical creep



Tobias and Johnston: Vet Surgery, 2018

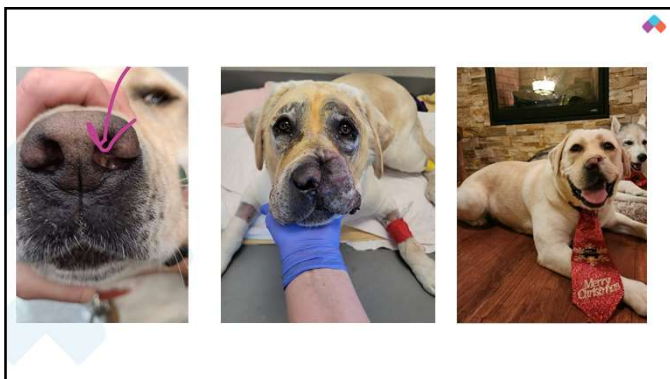


Photo Credit: Dr. Andrea Erickson




Surgical Dose: Radical Excision

- Curative intent
- Removal of an entire organ or structure
 - Amputation, hemipelvectomy
 - Splenectomy (cats)
 - Muscle removal
- No residual macro- or microscopic disease

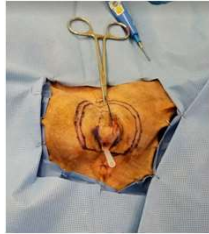



Principles of Surgical Oncology



Surgical Principles

- En bloc resection of biopsy tract - ALWAYS
 - FNA site of little consequence
 - Biopsy size minimized and oriented in a way that facilitates excision
- Early vascular ligation during mass removal
 - Venous versus arterial
- Margin of normal tissue indicated for local control
 - Do not enter pseudocapsule



Conclusions

- MCT can occur anywhere
 - 14% multiple tumors at diagnosis
 - Certain locations associated with worse prognosis
- Complete staging
 - Thoracic and abdominal imaging
 - FNA and cytology
 - +/-liver and splenic aspirates
 - Sentinel LN mapping
- Sentinel LN is often not the regional LN



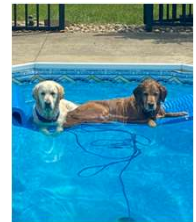
Surgical Principles

- Gentle tissue handling/tumor handling
 - Aggressive handling of tumor leads to tumor seeding
 - Copious lavage can remove small # exfoliated cells
 - This is NOT substitute for appropriate tissue handling
- Change gloves!
- Separate clean from dirty
 - Change gloves and instruments
 - Separate surgical packs for multiple tumors



Conclusions

- Surgical dose
 - Debulking/intracapsular
- Marginal
 - Planned marginal excision may be appropriate for limb salvage
 - Low recurrence rate (~11-14%)
- Wide excision
 - 2-3cm lateral margins and a fascial plane
 - Proportional margins appropriate for tumors <2cm
- Radical
 - Must stay out of the compartment or surgery ceases to be radical even if it is an aggressive procedure



Conclusions



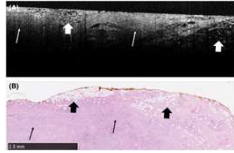
Conclusions

- Adjunctive treatments
 - Radiation therapy
 - Electrochemotherapy
 - Chemotherapy
- Communication with medical and/or radiation oncology
 - Follow-up and restaging



Future

- Use of optical coherence tomography to evaluate surgical margins
 - OCT had 90% sensitivity and 56.2% specificity in detection of incompletely excised MCT (*Dornbusch, Vet Comp Oncol, 2021*)
 - OTC identified MCT near the margin in 38.4%
 - *Cheng et al, Vet Comp Oncol, 2022* found an 86.7% sensitivity and 84.6% specificity for detecting incomplete margins in cutaneous and SQ tumors
- Promising for future "real-time" margin evaluation



Next up:

Updates on Medical Management of Canine MCT

