

Canine Mast Cell Tumors

When the chance to cut,
was not the chance to cure.....

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MEET THE MAST CELL

```
graph TD
    A[Multipotential hematopoietic stem cell (hematocytoblast)] --> B[Common myeloid progenitor]
    A --> C[Common lymphoid progenitor]
    B --> D[Erythrocyte]
    B --> E[Megakaryocyte]
    B --> F[Granulocyte]
    B --> G[Mast cell]
    E --> H[Thrombocytes]
    F --> I[Basophil]
    F --> J[Neutrophil]
    F --> K[Eosinophil]
    F --> L[Monocyte]
    L --> M[Macrophage]
    C --> N[Small lymphocyte]
    C --> O[Natural killer cell (large granular lymphocyte)]
    N --> P[B lymphocyte]
    N --> Q[T lymphocyte]
    P --> R[Plasma cell]
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WHAT IS THE PROBLEM WITH MAST CELL TUMORS?

Downs

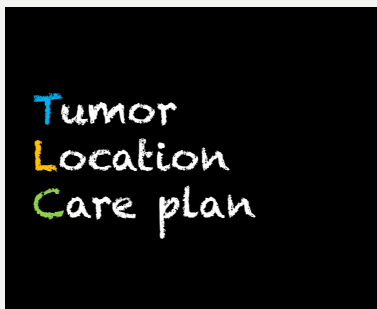
1. Any mass in any breed, age or location
2. Highly variable presentation
3. Highly variable behaviour
4. Many therapeutic options

Ups

1. Easy to diagnose
2. See 1
3. Predicting prognosis is tricky
4. Yes, but most cured with surgery ☺

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WHAT DOES AN ONCOLOGIST DO?



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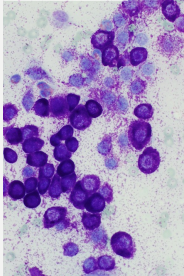
HOW TO DIAGNOSE A MCT?



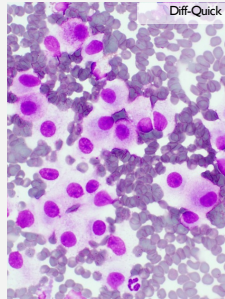
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DIAGNOSIS / CYTOLOGY

May-Grunwald Giemsa

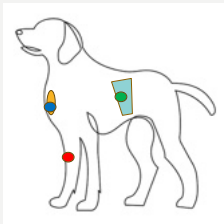


Diff-Quick



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LOCATION / STAGING



1. Tumor - T
2. Regional lymph node - N
3. Metastases - M (liver, spleen)

Goal

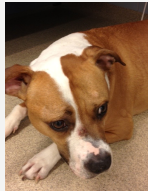
1. Prognosis prognosis
2. Guide further treatment

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T – WHAT DO WE LOOK AT?

T = only size, but keep an eye on

- Breed
- Location
- Number of tumors
- Growth rate
- Stage (metastases)
- Substage (clinical signs)
 - Tumor (erosion, ulceration)
 - Systemic (anorexia vomiting, diarrhea)
- Recurrence?

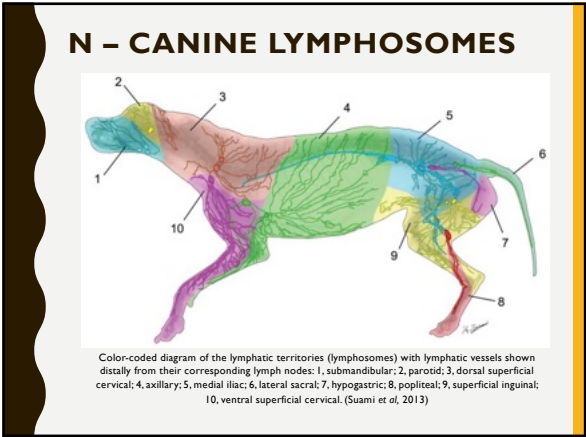


10-15% of dogs will develop multiple de novo MCTs



Cutaneous metastases

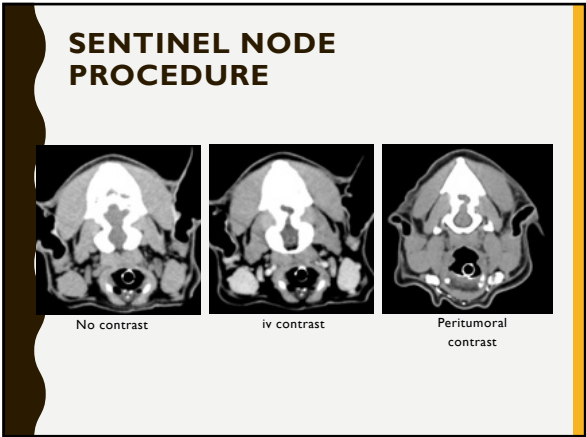
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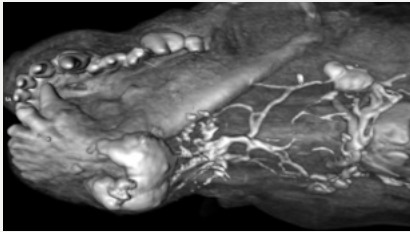


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SENTINEL NODE PROCEDURE



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STAGING - M

In case of high-risk MCT always

- Abdominal ultrasound
 - **always** FNAB liver and spleen
- In case of N+, next lymph node station
 - If possible FNAB

Not routinely indicated

- Bone marrow biopsy
 - Buffy-coat smear
 - Urinalysis
- Thoracic radiographs



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WHAT DOES A NORMAL ULTRASOUND EXAM TELL US?

Finding a normal liver, spleen or lymph nodes means very little.....
Sensitivity abdominal US for MCT metastases:
spleen 43%, liver 0%

So both in case of normal or abnormal, always perform a FNAB!
What is the problem?

Mast cells are everywhere in the body present,
and also in lymph nodes, liver and spleen

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SHOULD WE ALWAYS STAGE EVERY DOG WITH A MCT?

Medically speaking ,YES.....

ORIGINAL ARTICLE [Open Access](#)

Extensive staging has no prognostic value in dogs with low-risk mast cell tumours

Csilla Fejös, Karin Troedson, Natalia Ignatenko, Yury Zablotzki, Johannes Hirschberger

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WHAT MAKES IT A HIGH-RISK MCT?

- Tumor grade (Patnaik, Kiupel)
- Stage (lymph node metastasis)
- Growth rate
- Substage: ulceration
- Recurrence
- Location
 - Mucosal, Mucocutaneous
 - Preputium, Scrotum, Inguinal, Vulva
 - Ungual (nail bed)

Other factors frequently reported:

- Tumor size
 - < of $\geq$ 3cm
- Breed
- Number of tumors
 - 1 vs multiple vs satellites
- Substage
 - Systemic (anorexia, vomiting, diarrhea)

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THE MAJOR QUESTION IN ONCOLOGY

How do distinguish the good from the bad?
How do we tackle the problem?

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HOW TO DISTINGUISH THE GOOD FROM THE BAD?

- Resemblance to original cell type (differentiation)
- Tumor growth (proliferation)
- Chance to spread (metastasize)
- Chance to regrow following treatment (recurrence)
- Chance to develop multiple tumors (*de novo* tumor formation)

The diagram illustrates the relationship between different types of information and the resulting discrepancy in statistics. It features a central green box labeled 'Discrepancy (statistics = group vs individual)'. Above this box are four yellow boxes: 'Grade (pathologist)', 'Stage (clinician)', 'Proliferative indices (pathologist)', and 'Follow-up (clinician)'. Below the yellow boxes are two purple boxes: 'Information we (could ☺) have (prognostic factors)' and 'Information owner wants'. Arrows point from the yellow boxes to the purple boxes, and from the purple boxes to the central green box, indicating that the discrepancy arises from the difference between the information we could have and the information the owner wants.

Grade (pathologist)	Stage (clinician)	Proliferative indices (pathologist)	Follow-up (clinician)
Information we (could ☺) have (prognostic factors)		Information owner wants	
Discrepancy (statistics = group vs individual)			

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GRADING SCHEMES (3-2-4)

Figure 3 displays three graphs illustrating the Relative Distribution Function (Y-axis, 0.00 to 1.00) versus Time (days) (X-axis, 0 to 3000) for different grading schemes (3-2-4).

Graph 1: Shows the Relative Distribution Function for Grade I (green), Grade II (orange), and Grade III (red) curves. Grade I and II curves remain near 1.00, while Grade III drops sharply to approximately 0.15 by day 100.

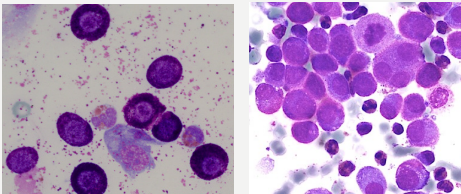
Graph 2: Shows the Relative Distribution Function for Low grade (green) and High grade (red) curves. The Low grade curve remains near 1.00, while the High grade curve drops sharply to approximately 0.25 by day 100.

Graph 3: Shows the Relative Distribution Function for Grade I - Low grade (green), Grade II - Low grade (orange), Grade II - High grade (blue), Grade III - High grade (red), and Subcutaneous (black) curves. The Subcutaneous curve remains near 1.00. Grade I - Low grade and Grade II - Low grade curves drop sharply to approximately 0.15 by day 100. Grade II - High grade and Grade III - High grade curves drop sharply to approximately 0.15 by day 100.

Sabatini et al., 2014



DIAGNOSIS / CYTOLOGY GRADING



well differentiated

Poorly differentiated

[illegible]

DIEGO



French bulldog MN 6½Y

First noted some months ago, growing for last 2 weeks. No systemic signs.

Cutaneous mass, 7 x 7 x 5mm, pink, alopecic, no other findings

RESULTS - I

Histopathology :

Macroscopy: An excisional biopsy measuring 35 x 12 x 17 mm, with a prominent dermal nodule of 5 mm in diameter.

Microscopy: A moderately well-defined, non-encapsulated, highly cellular dermal mass composed of mast cells with generally distinct basophilic granulation in the cytoplasm. The cells have a round, slightly eccentric nucleus with a small nucleolus, showing moderate anisokaryosis and atypia. The mitotic index is 1 per 10 high-power fields (400x). There is a scattered eosinophilic infiltration. The examined surgical margins are free of tumor cells (lateral margin of at least 4 mm, ventral margin of at least 3 mm).

Conclusion: ventral thoracic wall: Mastocytoma; Patnaik grade 2 (low grade), M1 1 per 10 HPF (400x) fields.

[illegible]

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[illegible]

ADVICE - 1

Comment:

Based on the Patnaik classification system, this tumor is histologically classified as an intermediate-grade mast cell tumor. Most mast cell tumors in dogs are classified as Grade 2. The biological behavior and prognosis of this large group of Grade 2 MCTs vary widely.

According to the more recent classification (Kiupel et al.), which only distinguishes between high and low grade, this is a low-grade MCT. Again, most MCTs fall into this low-grade group, and their biological behavior is variable; the median survival time is >2 years.

In addition to grading, other clinical factors specific to each patient should also be considered, particularly staging and the extent of tumor removal.

To better assess the prognosis of Grade 2/low-grade MCTs, we offer additional immunohistochemical staining applicable to formalin-fixed material. This includes the proliferation marker Ki-67 and the differentiation marker c-KIT.

If staining is required, please contact the helpdesk.

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RESULTS - 2

Immunohistochemistry:

The mast cell tumor diagnosed in this patient was stained with an antibody against Ki-67, a proliferation marker. Based on this staining **25/1000 positive** mast cells were found (= the Ki-67 index).

A grade 2 mast cell tumor (classified according to the Patnaik system) with a Ki-67 index < 93 has a cautious to favorable prognosis, and dogs with this tumor have a longer survival time than grade 2 tumors with a Ki-67 index > 93.

This tumor was also stained with an antibody against CD117 or c-KIT, a differentiation marker. Three c-KIT patterns have been described (where pattern I shows only membrane staining, pattern II shows membrane + cytoplasmic staining, and pattern III shows staining mainly perinuclear in the cytoplasm).

This mast cell tumor exhibits a **predominant KIT type II** staining pattern. This pattern is correlated with a shorter survival time and a higher chance of recurrence compared to a KIT type I mast cell tumor.

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ADVICE - 2

Comment:

Based on these two stainings, there is a **discrepancy between the results**.

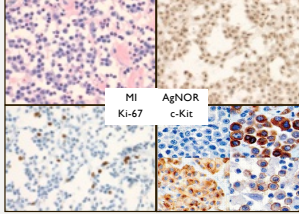
The question now arises: **does this tumor have a favorable or less favorable prognosis?** However, this question is not easy to answer. The literature states the following:

"Although the results of this study confirm the results of previous studies that have shown the prognostic significance of cellular proliferation in canine MCTs, cellular proliferation should not be evaluated as a single prognostic factor for canine MCTs but should be evaluated in tandem with additional prognostic markers such as histologic grade, c-KIT mutations, and aberrant KIT protein localization. To date, no single marker will definitively distinguish between benign and malignant MCTs. Therefore, each prognostic marker should be considered in light of additional markers in order to evaluate the full scope of the disease and to make the best therapeutic determinations for a given patient."

My advice is to consult an oncologist and, based on the **clinical picture** of this patient in combination with the histological grade and the immunohistochemistry results, determine an appropriate prognosis and therapy.

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WHAT DO THEY MEAN?



Markers for:

1. Proliferation: MI, Ki-67, AgNOR
2. Differentiation: Kit, does NOT predict
 - c-Kit mutation-status
 - best choice adjuvant therapy (TKI vs CT)

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AMY



Nova Scotia duck tolling retriever FN 7Y
subcutaneous mass on the buttock
15 cm diameter, not painful, not warm

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SUBCUTANEOUS MASTOCYTE TUMORS

No negative prognostic factors, excellent prognosis:

- 1- and 2-year survival: 90% and 77%

Negative PFs:

- Substage b (HR 10.44),
- Mitotic index >4 (HR 8.69),
- Use of (neo)adjuvant chemotherapy (HR 7.16)
- Multi-nucleated cells (HR 4.21)
- Older age (HR 1.29)



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JULIE



Jack Russell terrier FN 8Y
 Cutaneous mass on the right hind limb
 Recurrence of previously marginally
 excised Gr2/HG MCT, no metastases

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RADIOTHERAPY

Tumor size, (median progression-free survival / mPFS):

- Macroscopic: 12 months
- Microscopic: 54 months

Incomplete excision + adjuvant radiotherapy

- Grade 1: not routinely recommended
- Grade 2: 1- and 3-year survival 97% and 93%
- Grade 3: median PFS & overall survival 28 months



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MIKA



Shepherd mix M 8Y
 cutaneous mass on the hock (RA)
 and locoregional lymph node
 metastasis

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LOCOREGIONAL LYMPH NODE METASTASIS

Added value of good loco-regional tumor control in case of lymph node metastasis:
the risk of tumor progression and tumor-related death was 2-5x and 3.6x higher in the group that did not have lymph node excision

Prognosis following lymphadenectomy

- Gr2 N+/M- as good as Gr2 N-/M-
- Gr3 most likely better, but not as good as for Gr2

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CHEMOTHERAPY – MACROSCOPIC SETTING

Drug protocol	n	Response (%)			Response duration (d)
		Total	Complete	Partial	
Prednisolone	25	20	4	16	NR
Vincristine	27	7	0	7	NR
Vinblastine	51	12-27	0-4	12-23	23-77
CCNU	23	44	6	38	79
COP - Hydroxyurea	17	59	23	35	53
Cyclophosphamide - Vinblastine - Prednisolone	11	63	29	35	74
Vinblastine - Prednisolone	18	47	33	13	154
CCNU - Vinblastine - Prednisolone	17	64	29	35	52
Chlorambucil - Prednisolone	21	38	14	24	533

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CHEMOTHERAPY – MICROSCOPIC SETTING

Drug protocol	n	Survival		PFS (d)
		1-year (%)	2-year (%)	
Cyclophosphamide - Vinblastine - Prednisolone	17	-	-	489
Vinblastine - Prednisolone	23	57	57	-
Vinblastine - Prednisolone	61	-	-	1.305
CCNU - Vinblastine	20	-	-	245
CCNU - Vinblastine - Prednisolone	37	-	-	489

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LUCKY

Cocker spaniel FN 10Y8M

Mastcell tumor hind limb (LA) Gr3/HG - Stage 4

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C-KIT AND MASTCELL TUMORS

- c-Kit is a growth factor receptor of the tyrosine kinase receptor type
- Mast cell tumors often have an activating mutation in c-Kit
- TKRs can be blocked with drugs TKIs
 - Masivet - masitinib
 - Palladia - toceranib

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C-KIT AND MAST CELL TUMORS

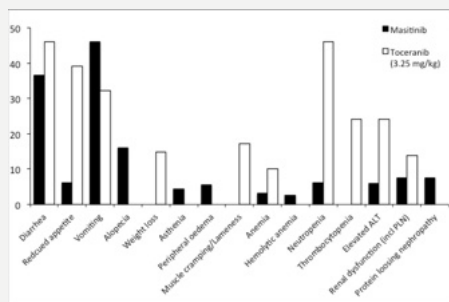
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AFTER 2 WEEKS MASIVET



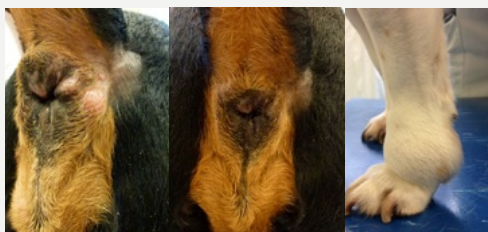
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TOXICITY



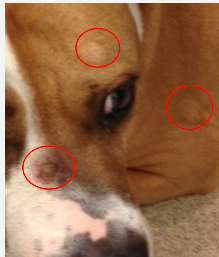
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WHEN DO I USE TKIs?



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DEVIL



American Staffordshire M 5Y
cutaneous massa on the nose
2cm, not painful, not warm

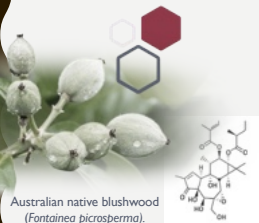
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IS THERE ANYTHING NEW?



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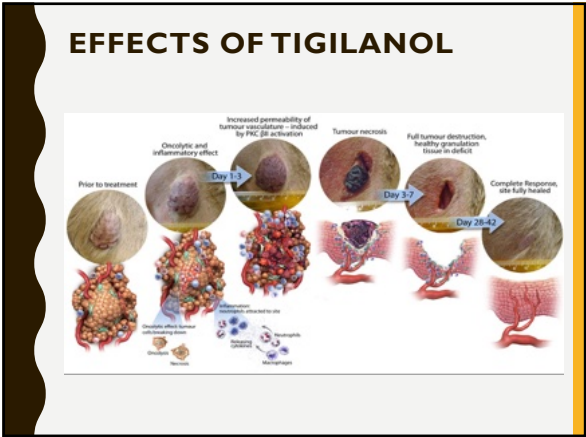
TIGILANOL-TIGLATE



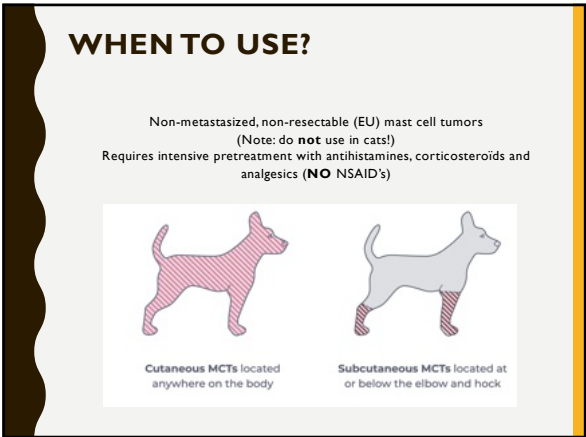
Australian native blushwood
(*Fontainea picrosperma*).

- EBC-46 from the blushwood berrie
- Small molecule, agent protein kinase C activator
- Multiple mechanisms:
 - Direct oncolysis tumor cells through mitochondrial damage
 - Induces an acute inflammatory response compromising tumor blood- and oxygen supply
 - Activates the innate immune response
 - Increases permeability tumor vasculature

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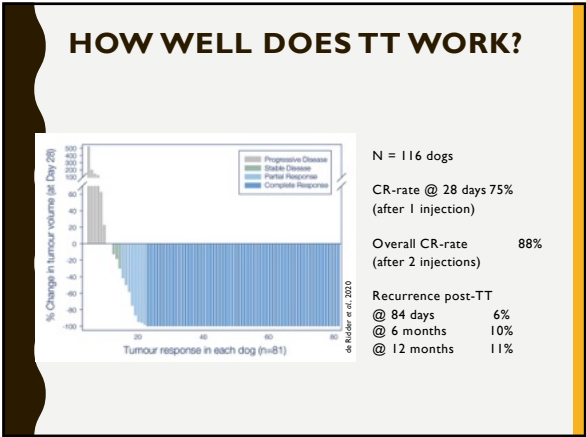
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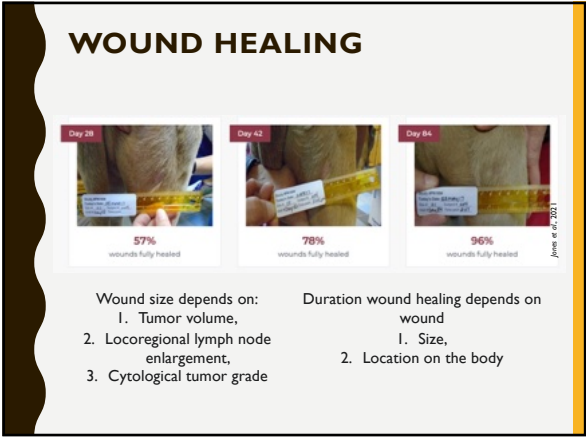
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