Small Animal Oncology Basics for the Dermatologist

Carine Laporte, VMD, DACVD

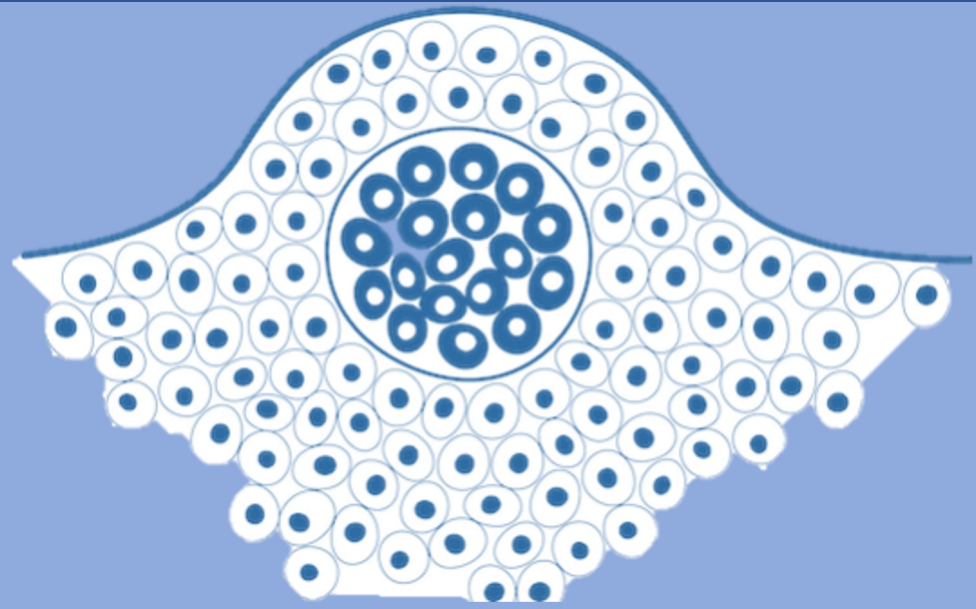
Oncology Basics

GOALS:

1. Re-familiarize with oncology concepts and common terms
2. Specific cutaneous round cell tumor syndromes in dogs and cats

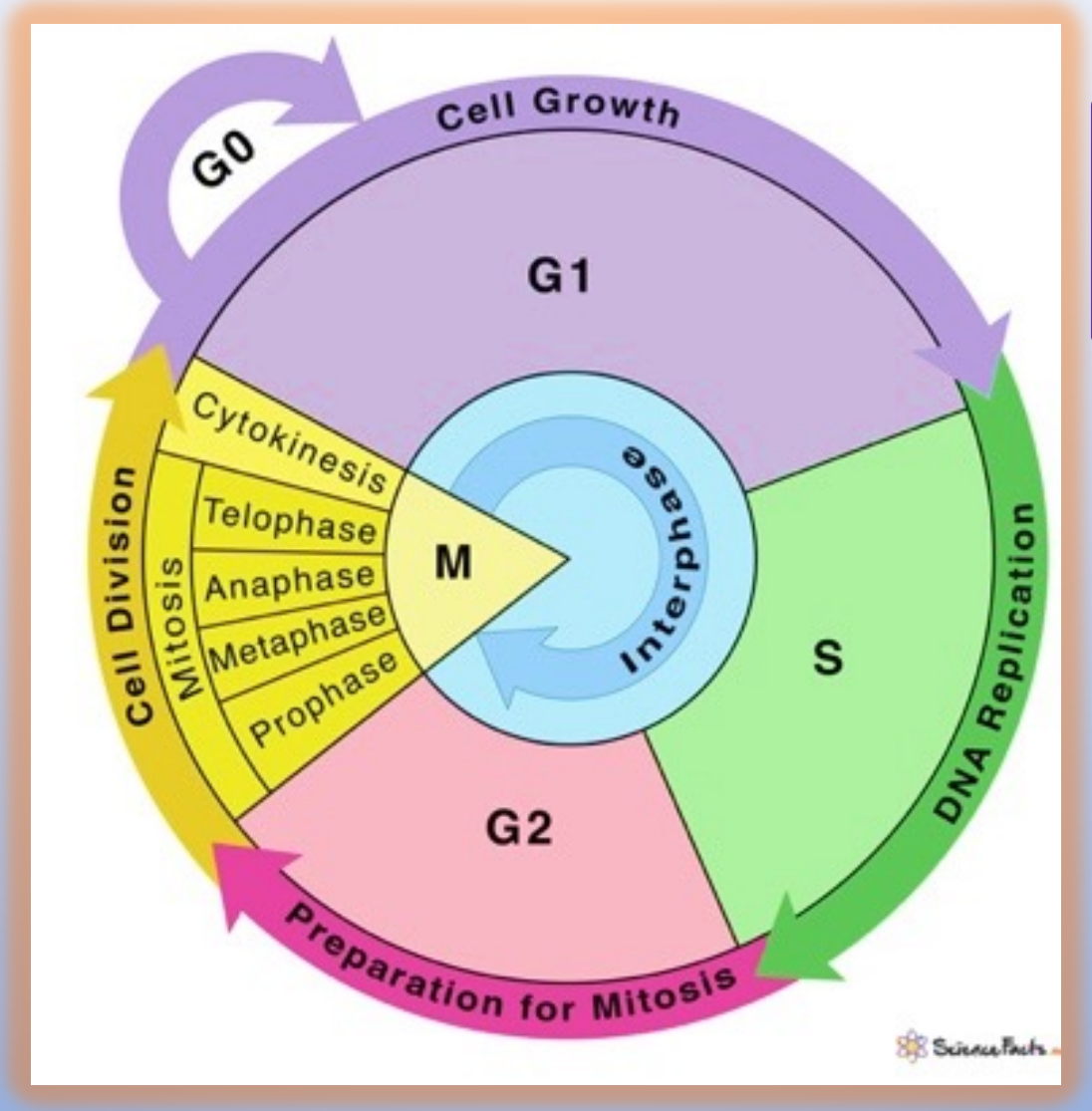
Oncology Basics

Neoplasia:



Uncontrolled growth of cells leading to a phenotypic expression which can range from mild to life threatening.

Cell Cycle



Finely coordinated

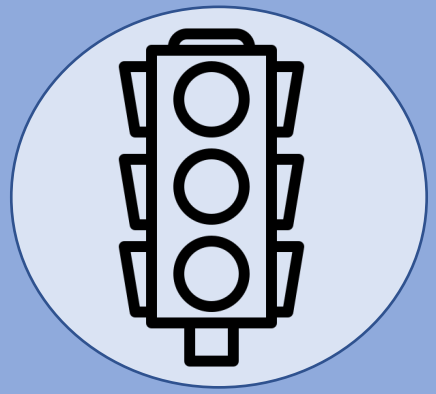
Highly regulated

Controlled cell growth

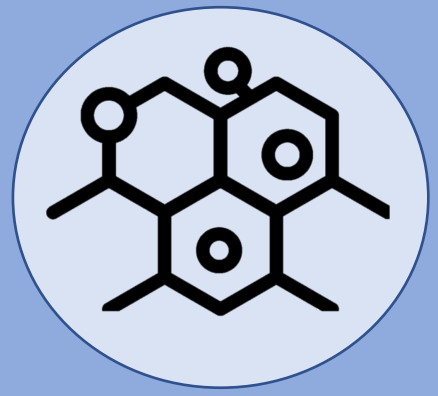
Accurate DNA replication

Cell Cycle

How does the cell cycle prevent neoplasia?

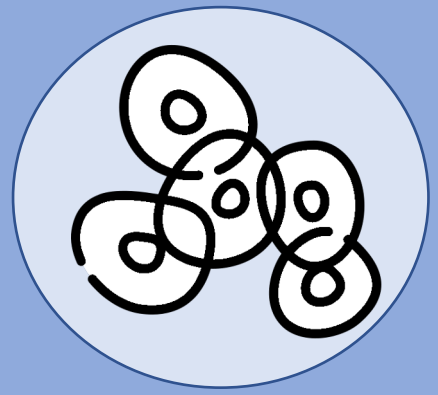


Checkpoints



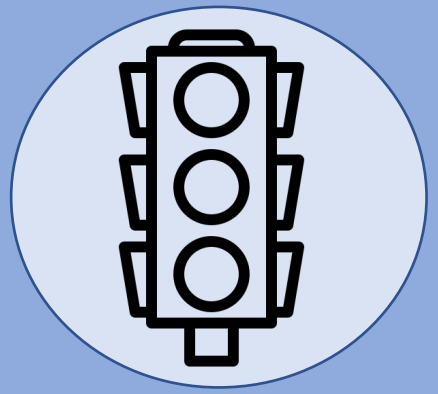
Chemical and Protein Signals

Telomeres

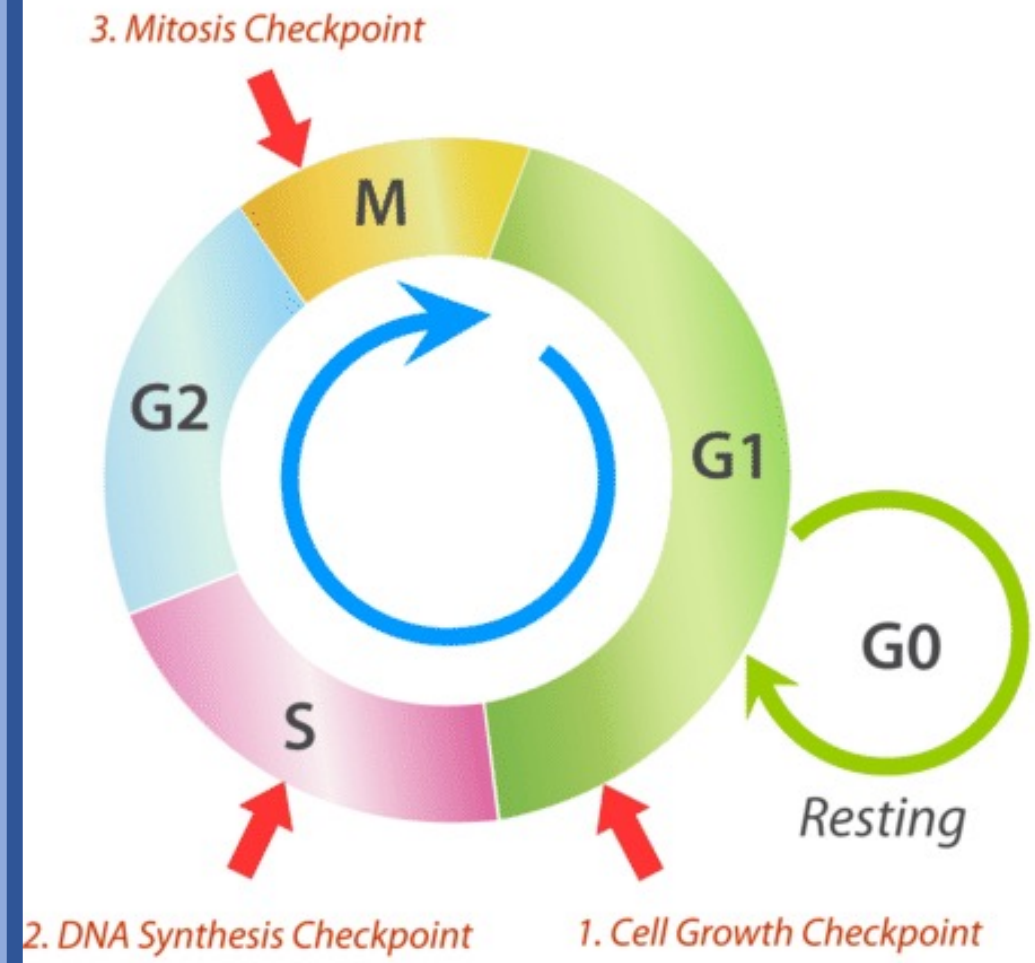


Contact Inhibition

Prevention of Cancer



Checkpoints



1. Cell Growth Checkpoint

- Occurs toward the end of growth phase 1 (G1).
- Checks whether the cell is big enough and has made the proper proteins for the synthesis phase.
- If not, the cell goes through a resting period (G0) until it is ready to divide.

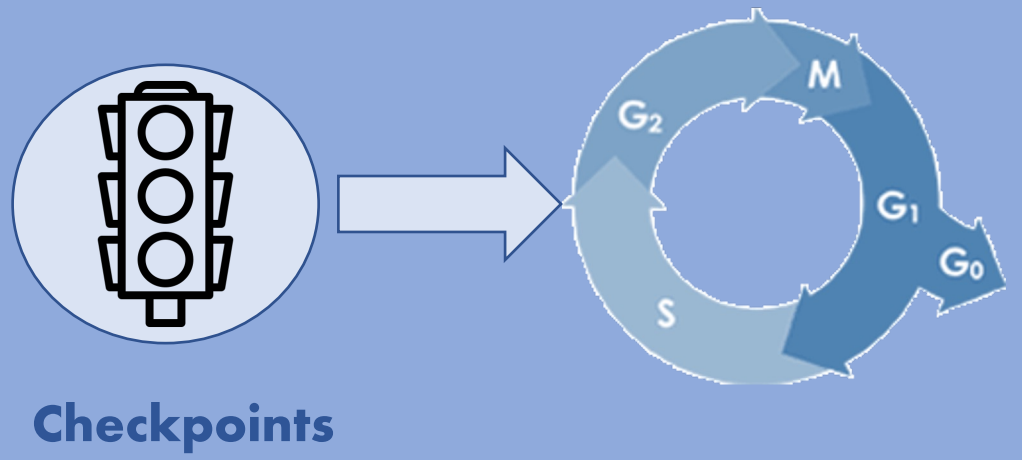
2. DNA Synthesis Checkpoint

- Occurs during the synthesis phase (S).
- Checks whether DNA has been replicated correctly.
- If so, the cell continues on to mitosis (M).

3. Mitosis Checkpoint

- Occurs during the mitosis phase (M).
- Checks whether mitosis is complete.
- If so, the cell divides, and the cycle repeats.

Prevention of Cancer

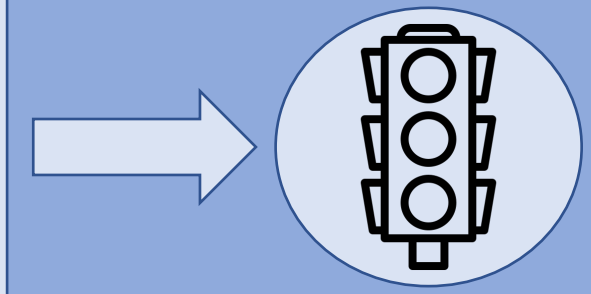


Checkpoints

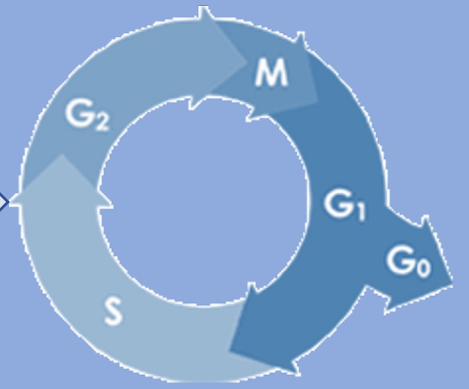
Prevention of Cancer

Regulators of checkpoints:

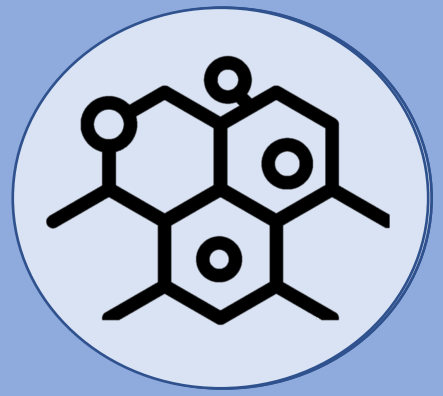
1. **Cyclins**
2. **Cyclin dependent kinases**
3. **Anaphase-promoting complex / cyclosome (APC/C)**



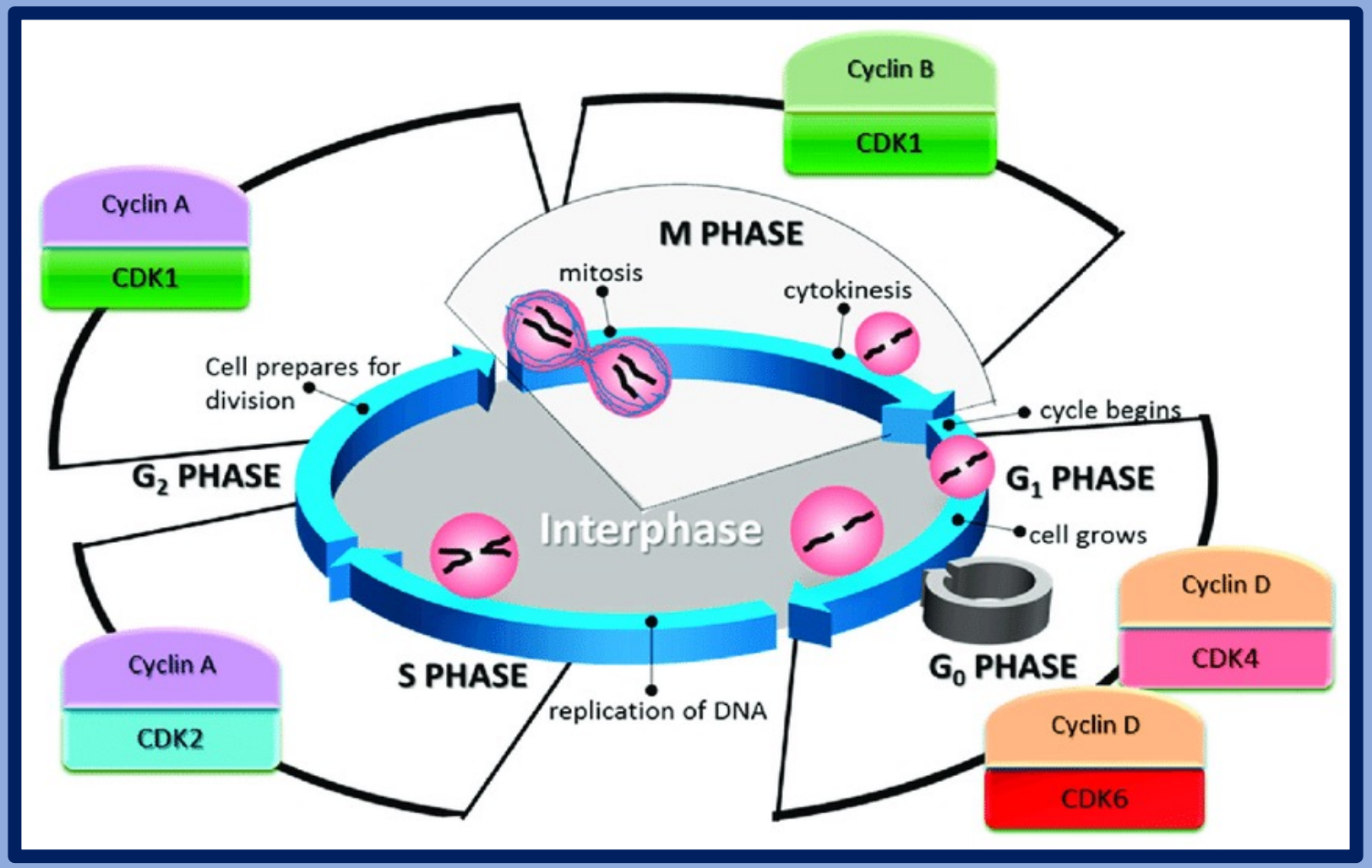
Checkpoints



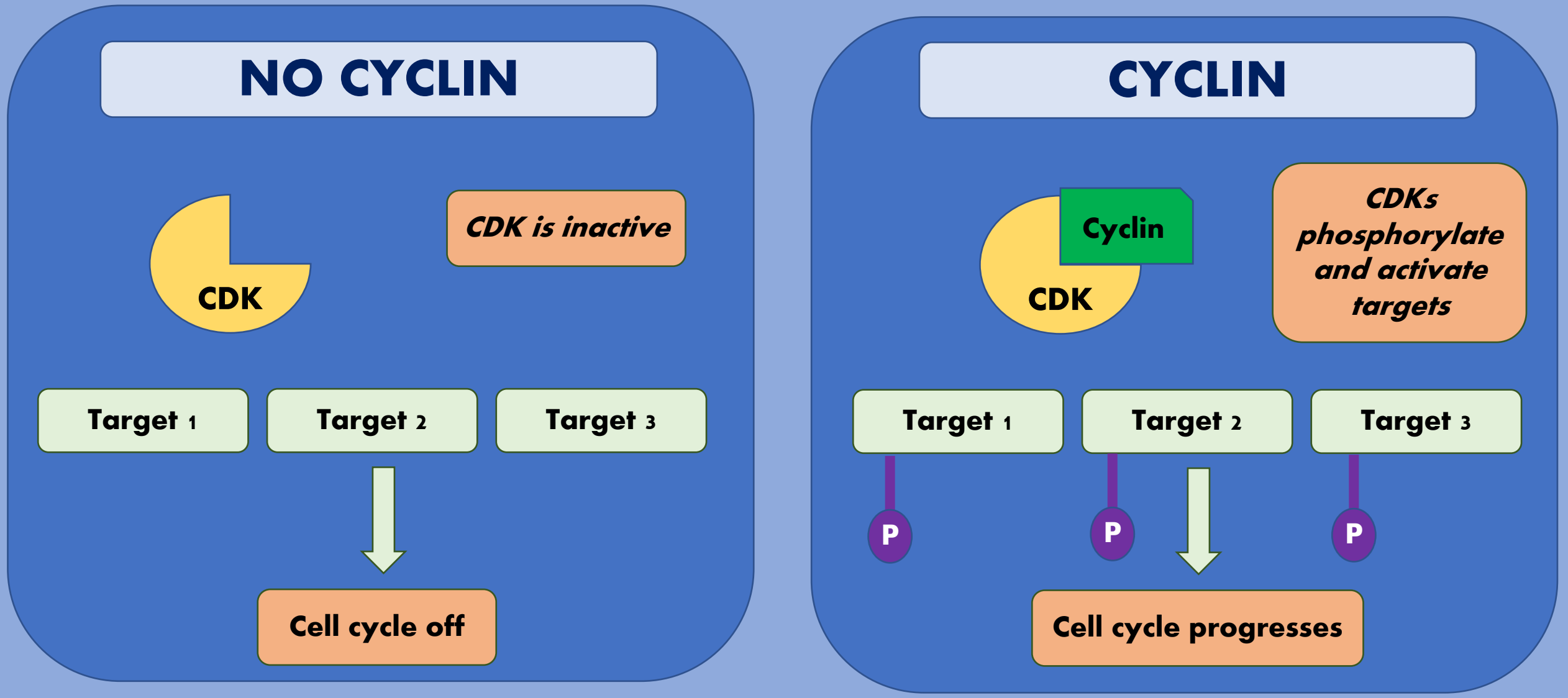
Cyclins



Chemical and Protein Signals



Cyclins

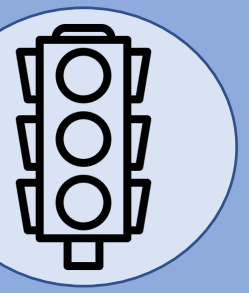

NO CYCLIN
CDK
CDK is inactive
Target 1
Target 2
Target 3
Cell cycle off
CYCLIN
Cyclin
CDK
CDKs phosphorylate and activate targets
Target 1
Target 2
Target 3
P
P
P
Cell cycle progresses

Prevention of Cancer

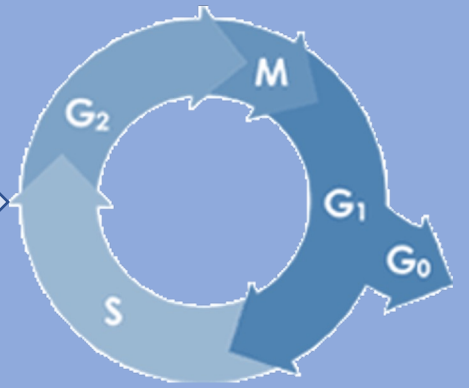
Regulators of regulators of checkpoints:

- **Positive cues**
- **Negative cues**

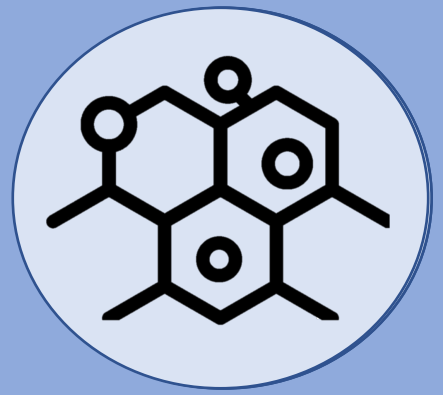
Regulators of checkpoints



Checkpoints



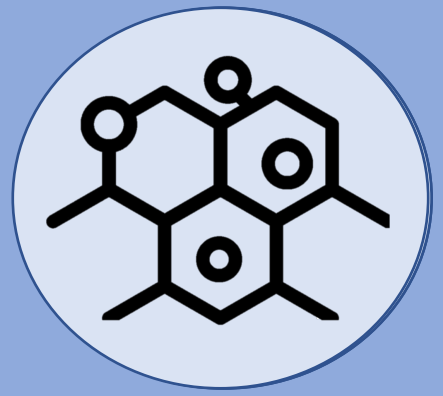
Positive Cues



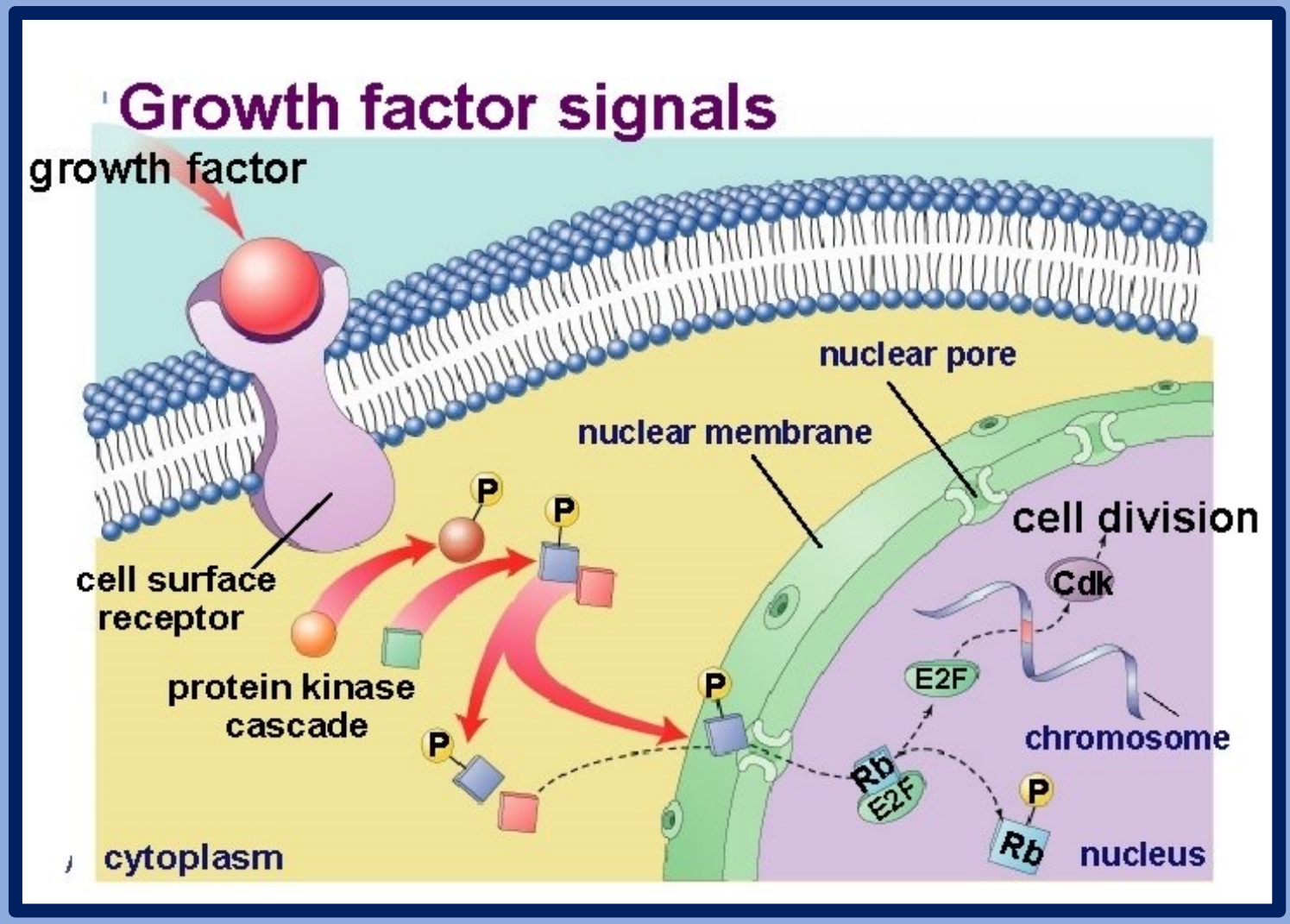
Chemical and Protein Signals

- **Growth factors**
- **Hormones**

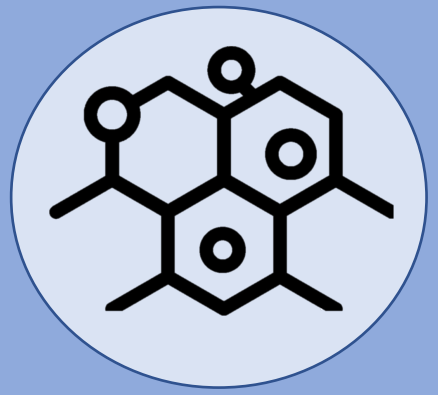
Growth Factors



Chemical and Protein Signals



Negative Cues



Chemical and Protein Signals

DNA damage
Cell cycle abnormalities
Hypoxia

Mdm2

p53

p53

Cell cycle arrest

DNA repair

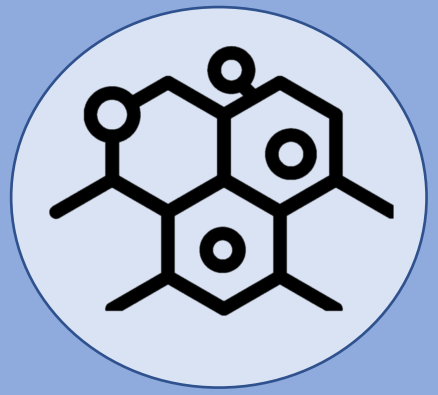
Cell cycle restart

Apoptosis

Death and elimination of damaged cells

Cellular and genetic stability

Negative Cues



Chemical and Protein Signals

DNA damage
Cell cycle abnormalities
Hypoxia

Mdm2

p53

p53

Cell cycle arrest

DNA repair

Cell cycle restart

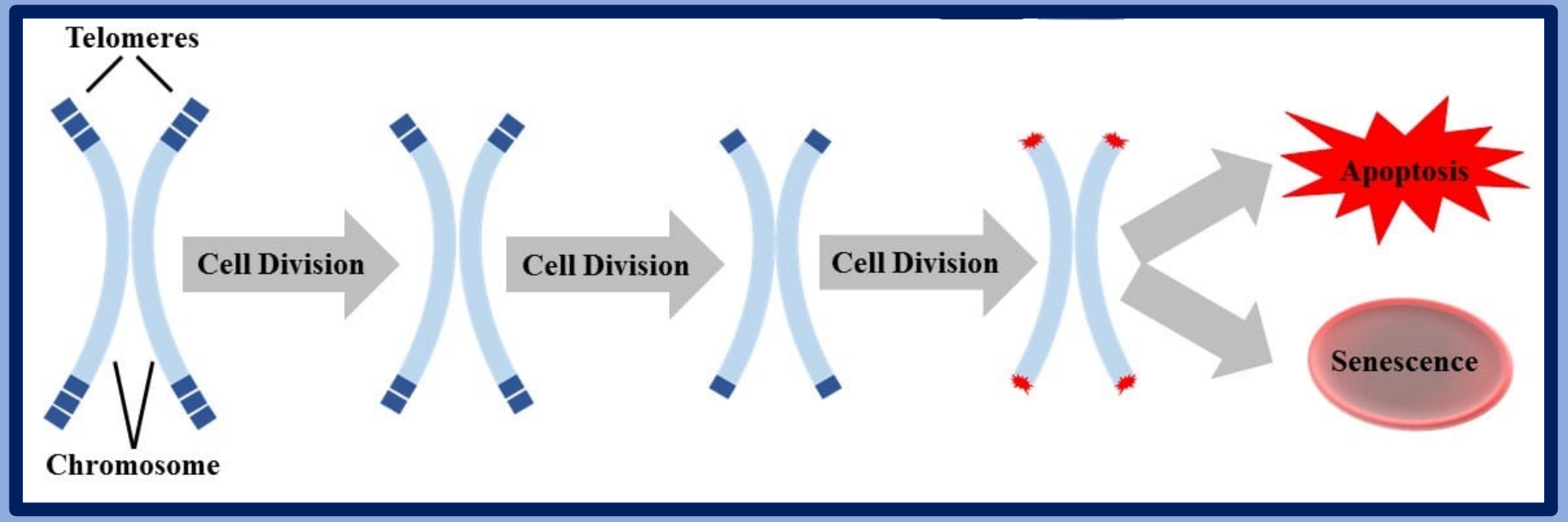
Apoptosis

Death and elimination of damaged cells

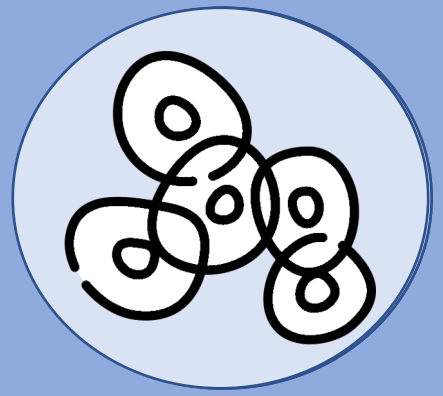
Cellular and genetic stability

Prevention of Neoplasia

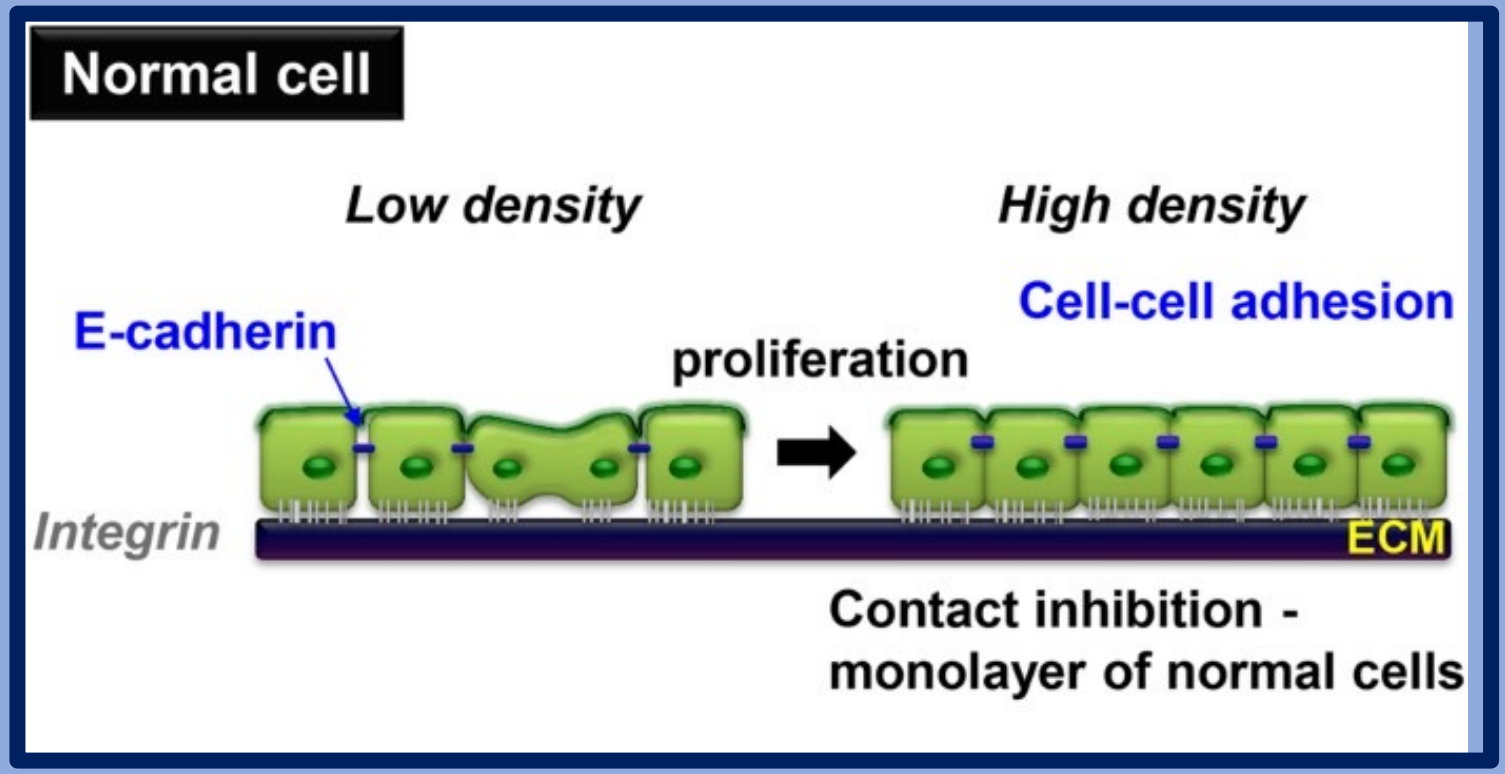
Telomeres



Prevention of Neoplasia



Contact Inhibition



Development of Neoplasia

How does a cell become Neoplastic?

1. Loss of normal checkpoints

2. Loss of control of chemical and protein signals

5. Loss of contact inhibition

3. Loss of signal to die (telomeres)

4. Loss of normal repair mechanisms in S phase

UNCONTROLLED CELL GROWTH

Development of Cancer

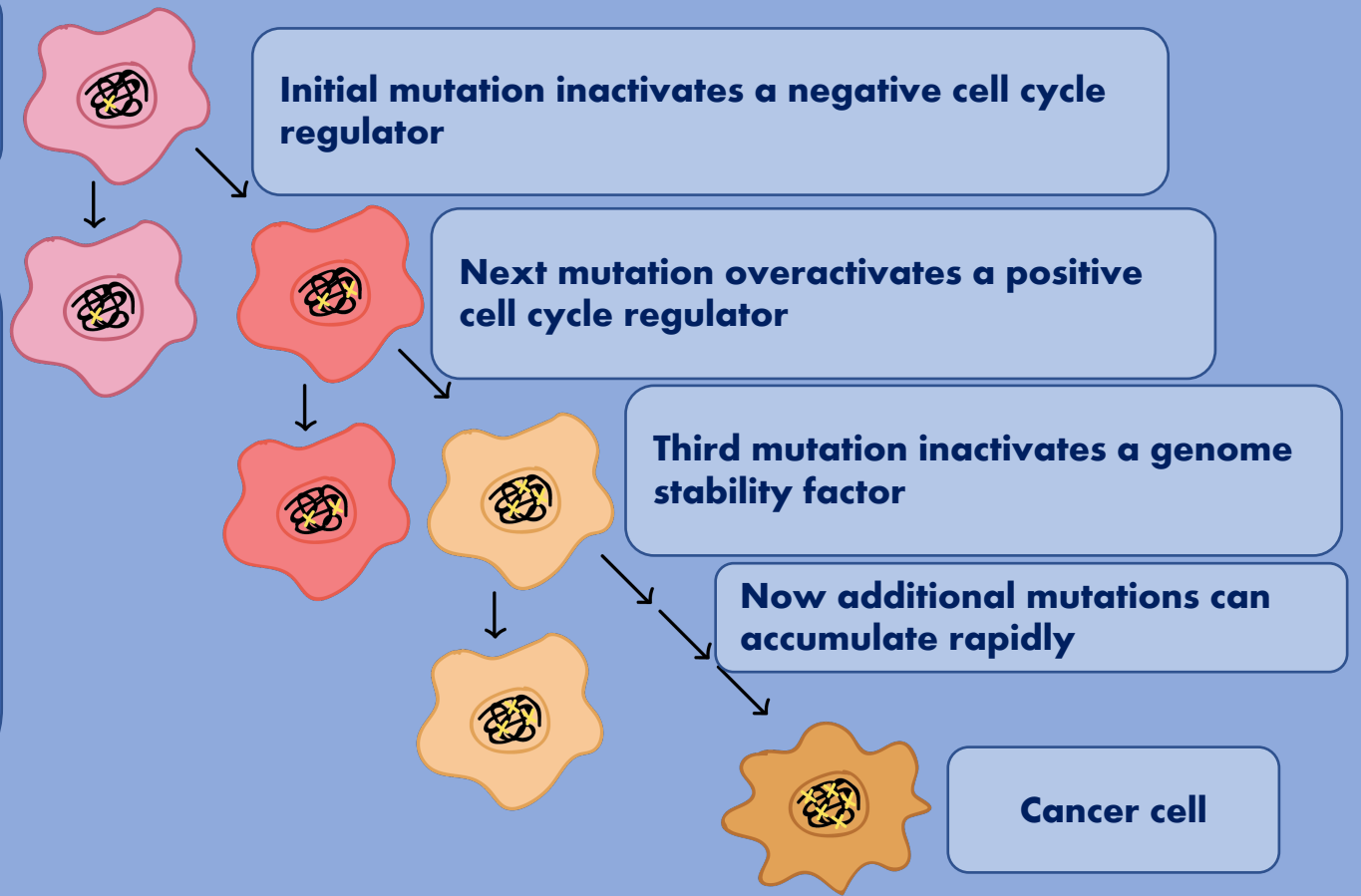
What kinds of mutations dysregulate the cell cycle?

Multistep process
Multiple mechanisms must fail

Most cancers are due to series of mutations that make the cells:

- **Divide more quickly**
- **Escape internal and external controls on division**
- **Avoid programmed cell death**

Hypothetical series of events leading to cancer

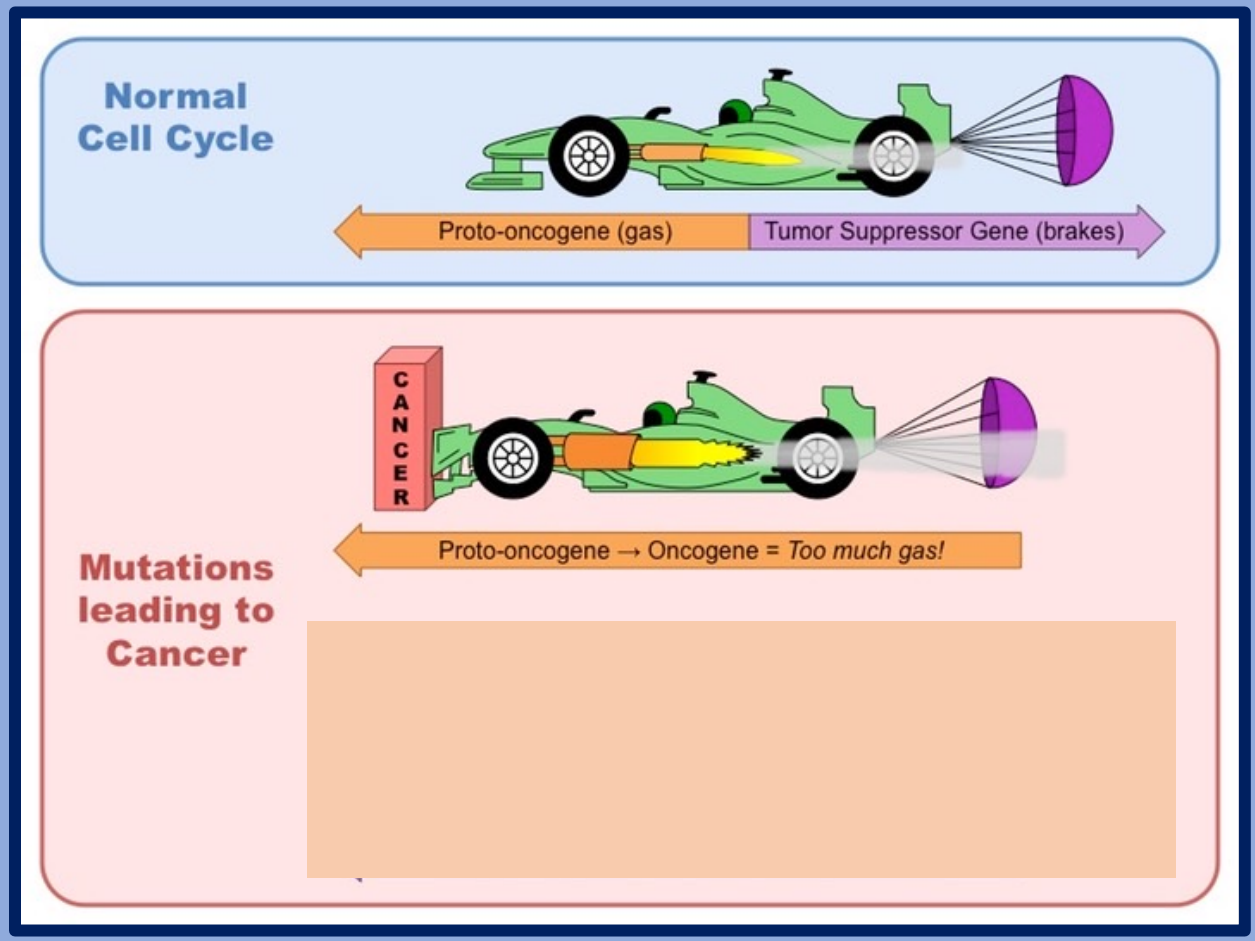


Development of Cancer

What kinds of mutations dysregulate the cell cycle?

Proto-oncogene (not mutated)
→ Oncogene (mutated)

- **Usually positive cell regulators**
- **Examples: genes for**
  - **growth factor receptors**
  - **cyclins**
  - **cyclin-dependent kinases**



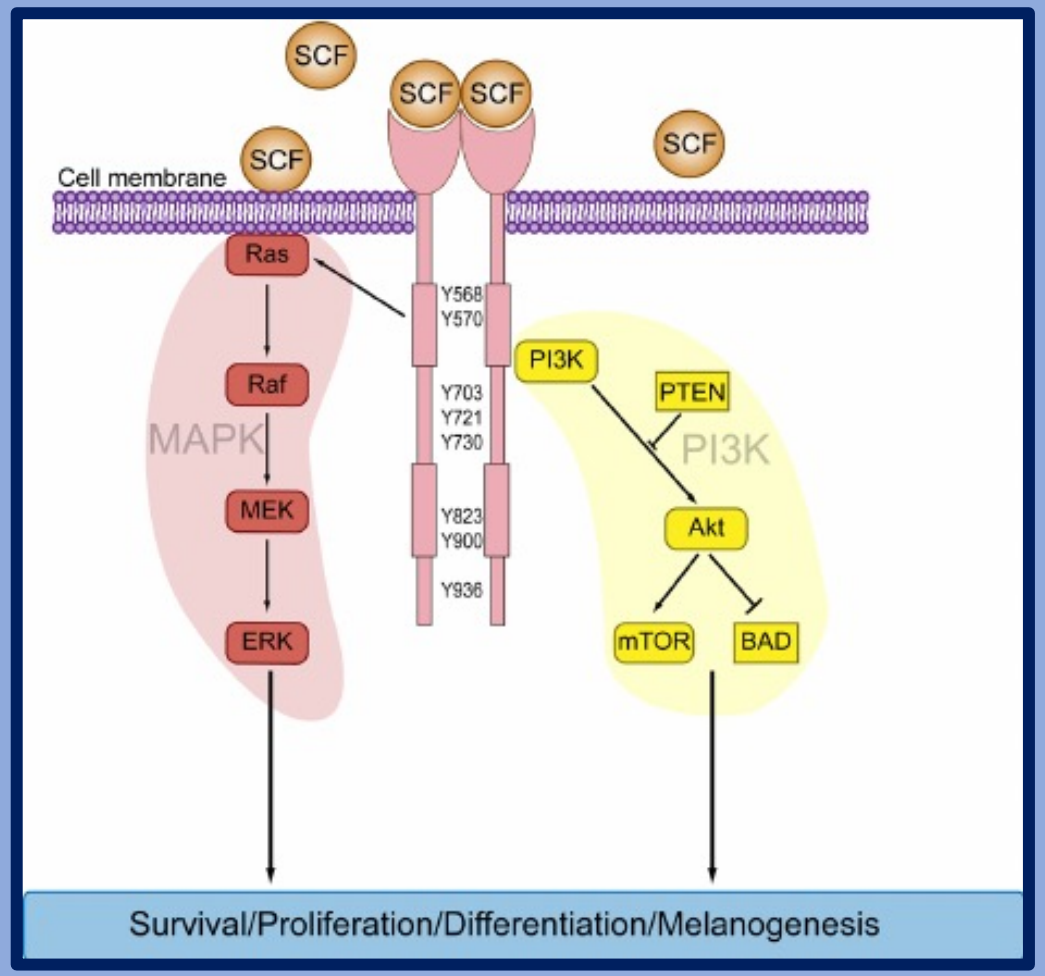
Development of Cancer

What kinds of mutations dysregulate the cell cycle?

Proto-oncogene (not mutated)
→ Oncogene (mutated)

Major example in vet med:

c-kit

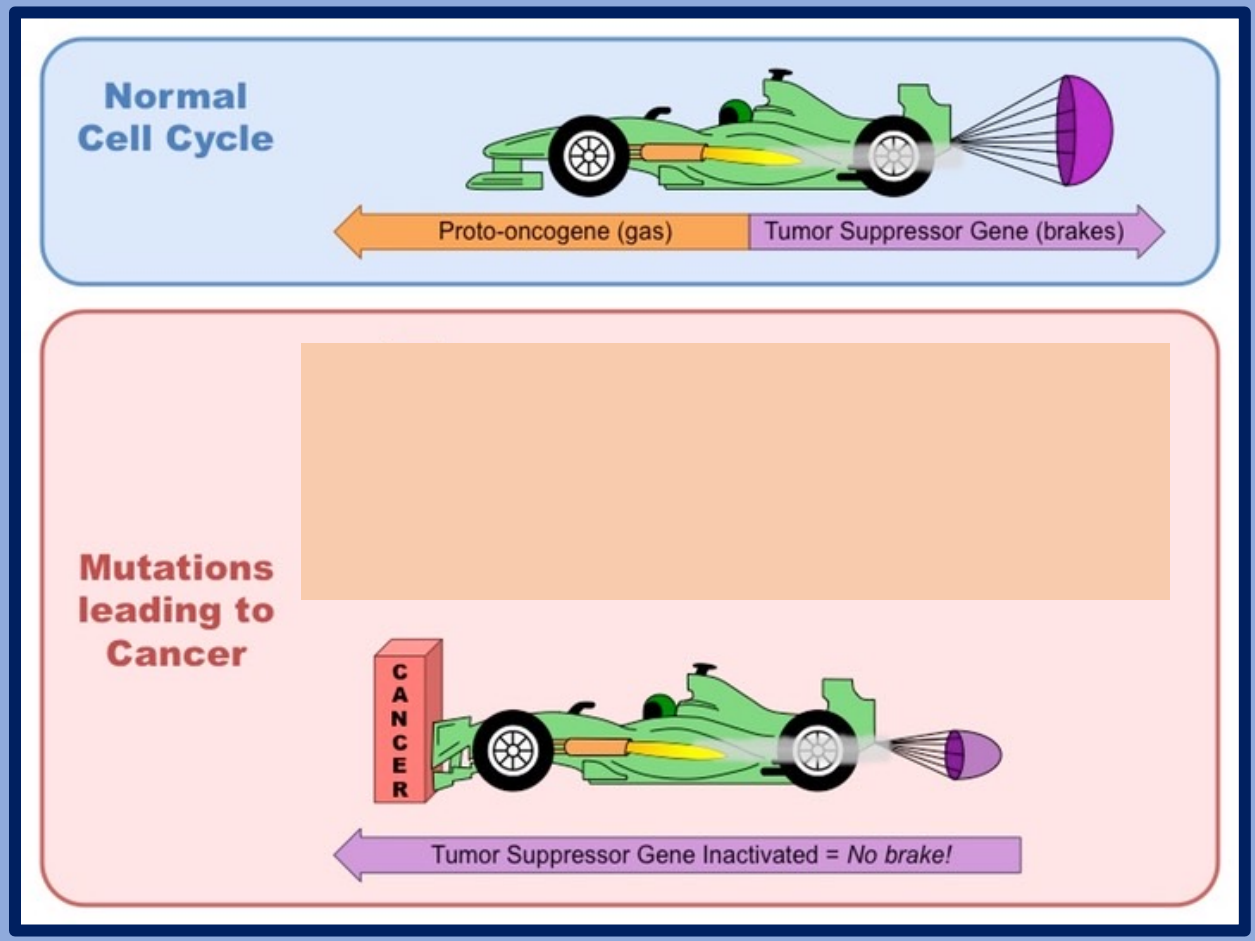


Development of Cancer

What kinds of mutations dysregulate the cell cycle?

Tumor Suppressor Genes

- Usually negative cell regulators
- Examples:
  - p53
  - pRb
  - p16



Carcinogenesis

- Genetics
- Obesity
- Acquired environmental DNA damaging agents)
  - Chemicals
  - Radiation (UVB!)
  - Viruses

Normal cell

DNA damage

Successful DNA repair

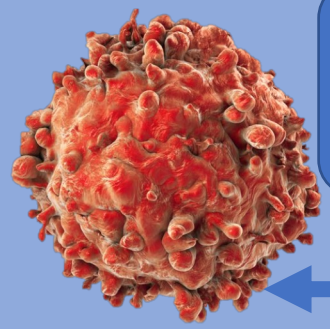
Failure of DNA repair

Mutations in somatic cell genomes

Activation of growth promoting oncogenes

Alterations of genes that regulate apoptosis

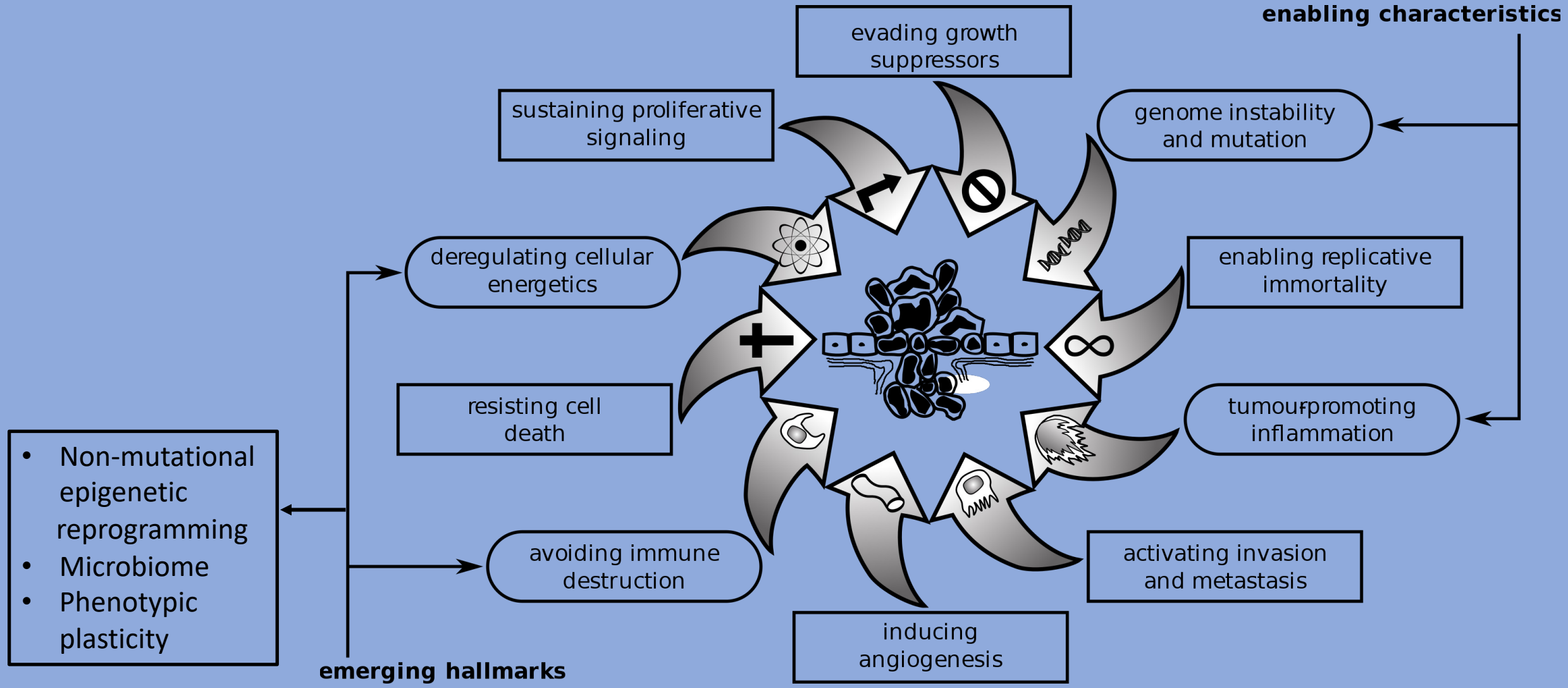
Inactivation tumor suppressor genes



- Clonal expansion
- Additional mutations
- Heterogeneity

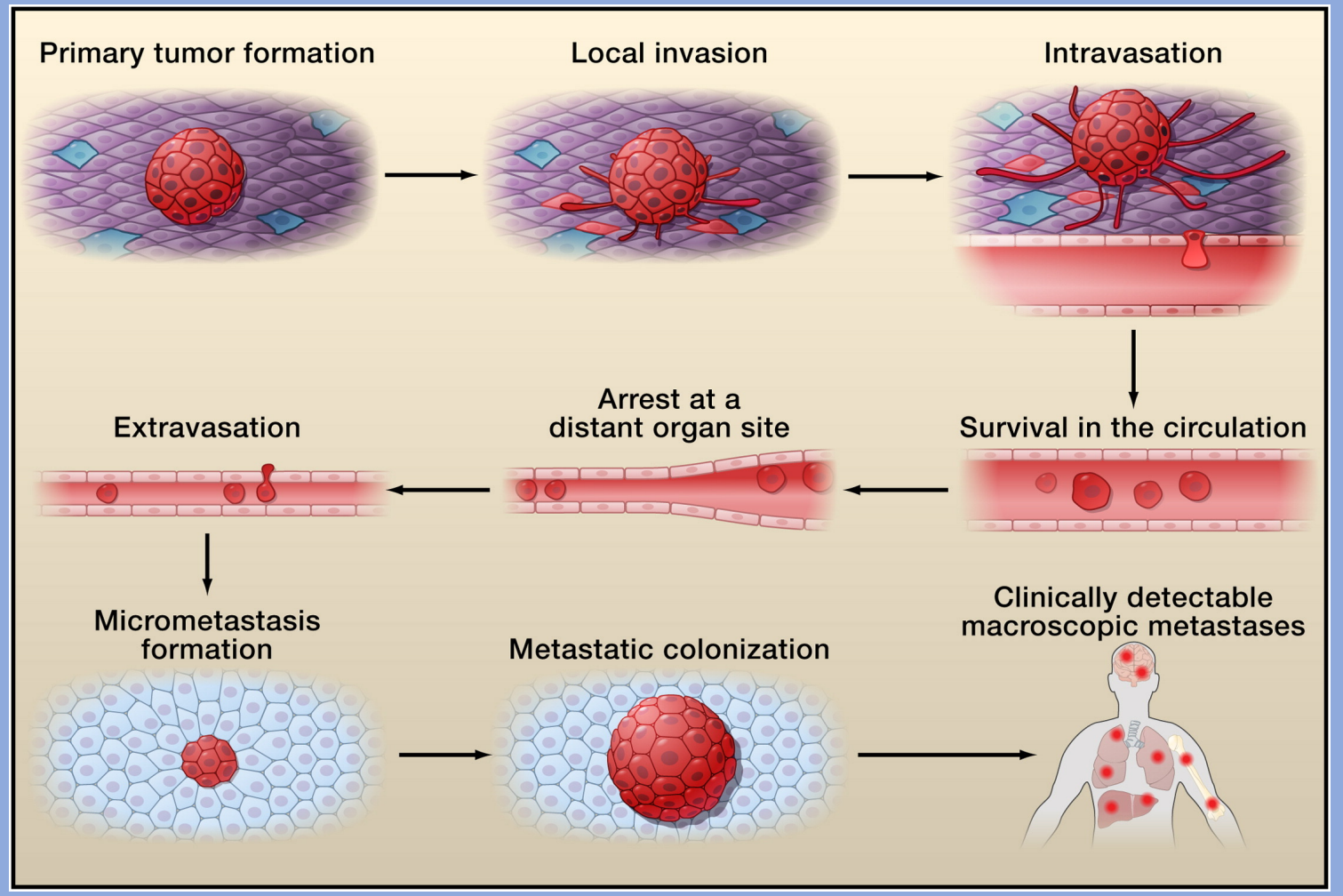
- Expression of altered gene products
- Loss of regulator gene products

Hallmarks of Cancer



Metastatic Cascade

Metastasis:
The development of secondary tumors at a site distant from the primary tumor site.

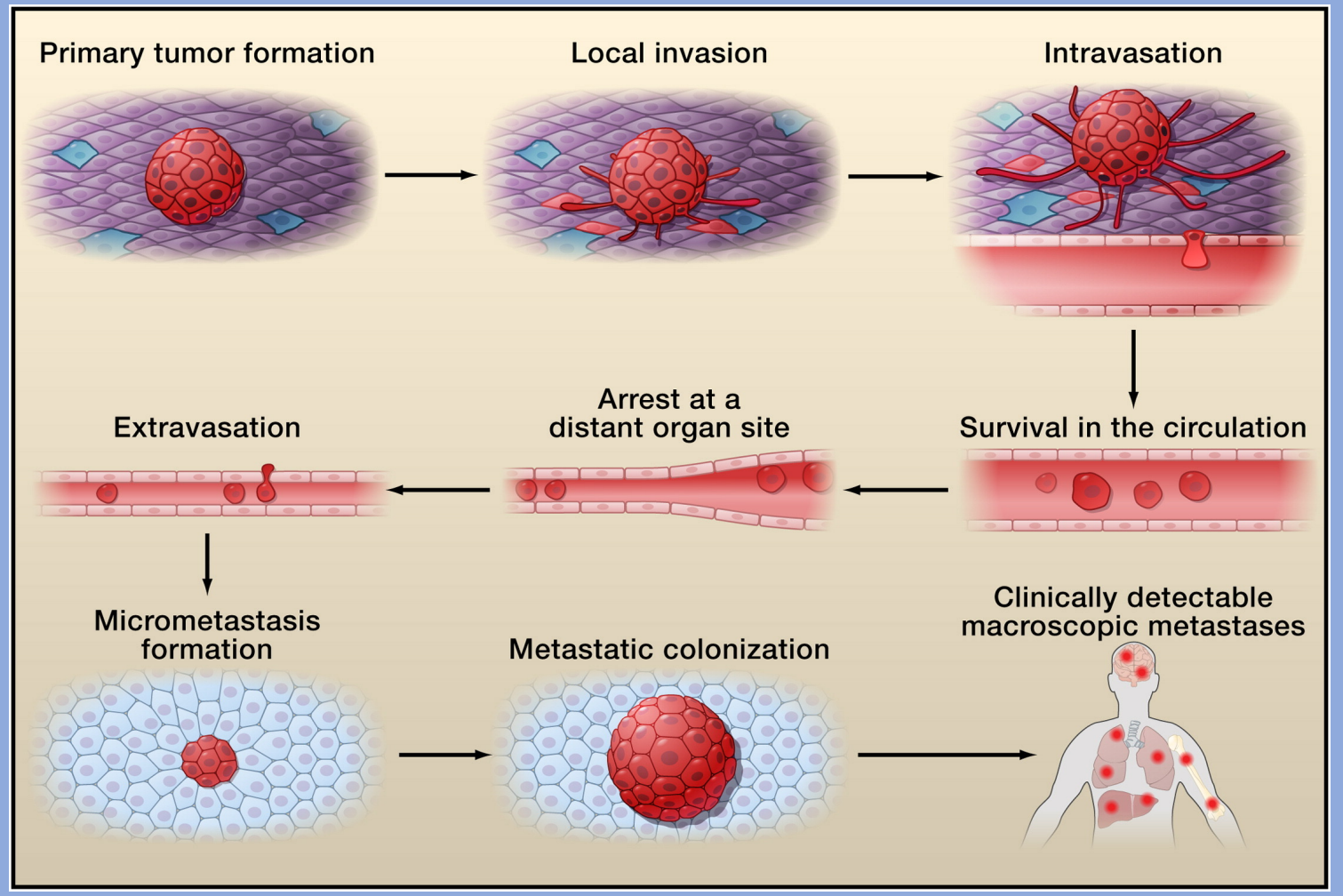


Metastatic Cascade

Anoikis:

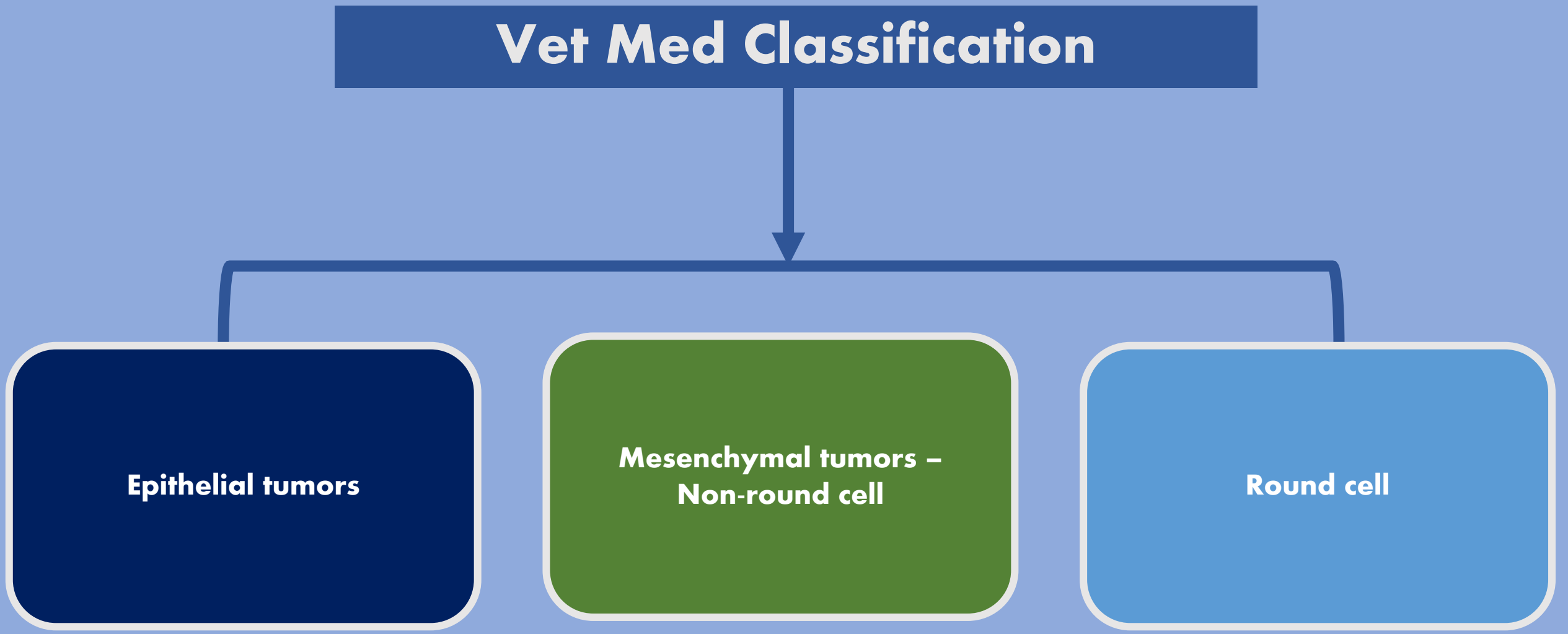
- ***Programmed cell death occurring upon detachment from the correct extracellular matrix.***
- ***Type of apoptosis.***
- ***Protects against metastasis.***

Cancer cells can develop resistance to anoikis → Contributes to metastasis.



Tumor Classification

Vet Med Classification



Tumor Classification

Vet Med Classification

FYI!
Round cells technically are mesenchymal cells

- Epithelial tumors
- Mesenchymal tumors – Non-round cell
- Round cell

Melanomas are technically neural crest origin but often grouped as round cell

Epithelial Tissues

Characteristics

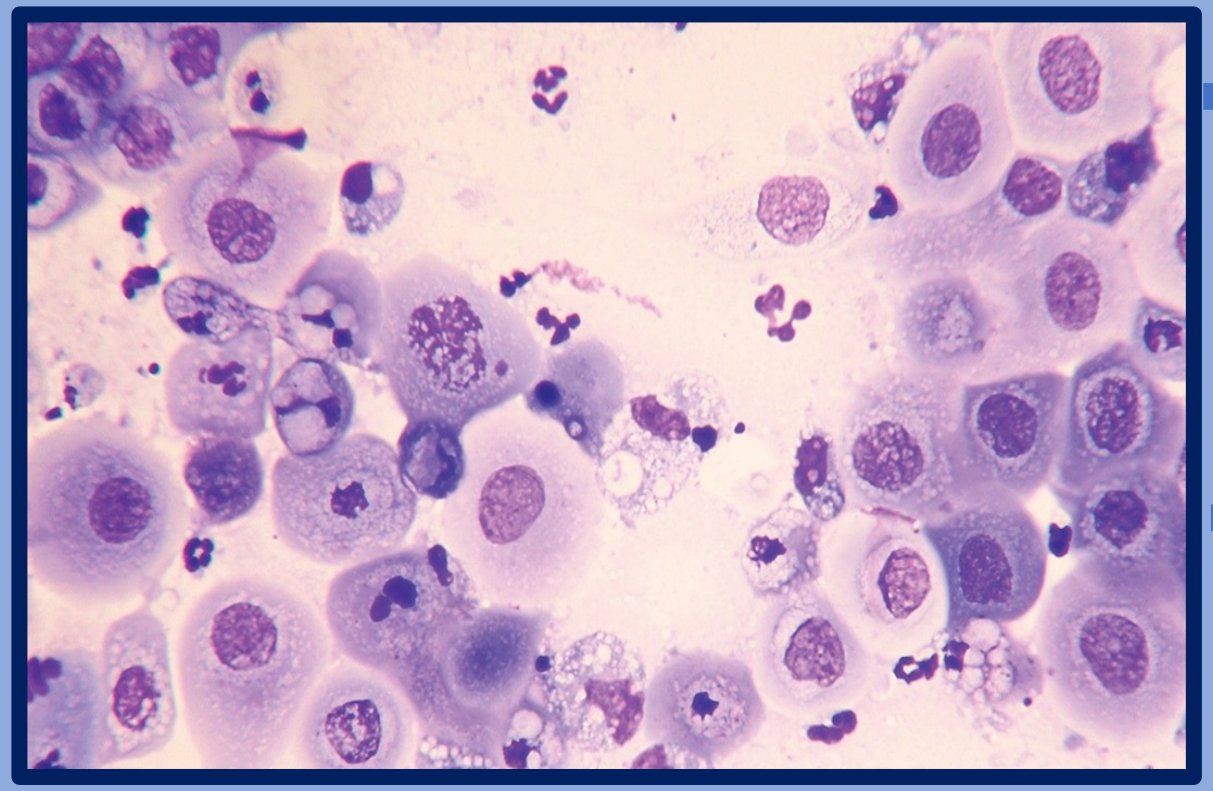
- Cover exposed body surfaces
- Also around heart, lungs, urogenital tract, brain, spinal cord

- Cytoskeletons
- Cells are closely adhered to each other

- Epithelial tissue in the skin:
  - Epidermis
  - Hair follicle
  - Cutaneous glands

Epithelial Tumors

Characteristics



- Primary tumors – any location lined by epithelium
- Metastatic tumors – non-epithelial tissue possible

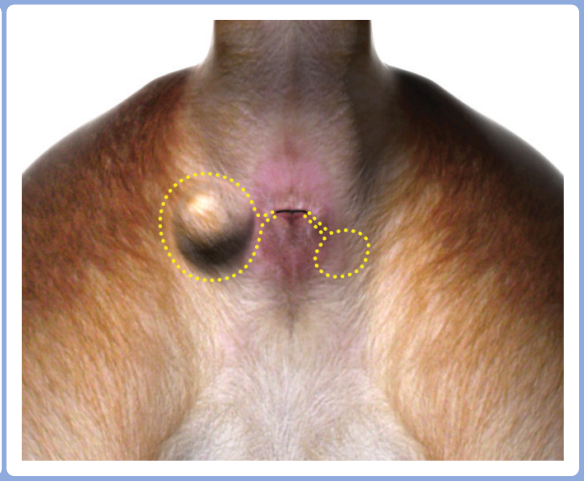
- Benign tumors = –oma
- Malignant tumors = –carcinoma
- Gland tumors = adeno-

Epithelial Tumors

Examples

Squamous Cell Carcinoma

Sebaceous Adenoma



Apocrine Tumors

Mesenchymal Tissues

Characteristics

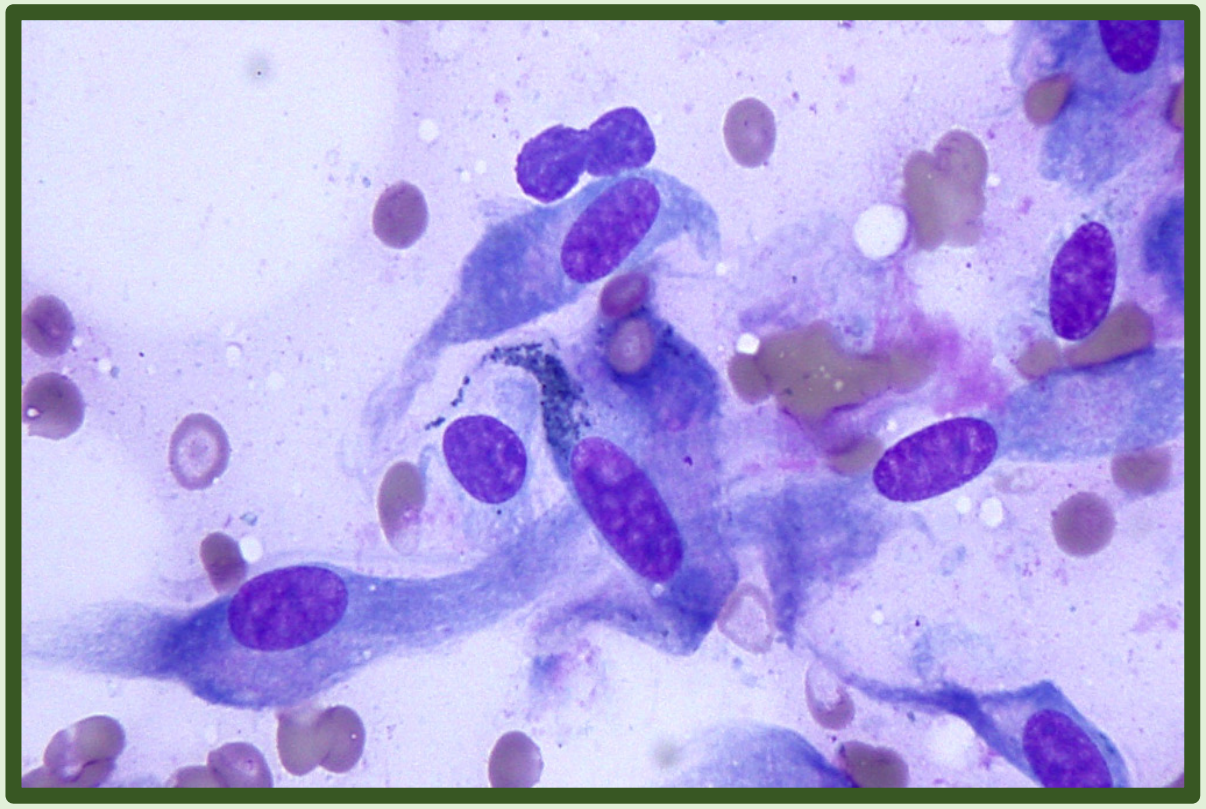
- In many organs, give shape and strength
- Mesenchymal cells develop into vessels and connective tissue

- Major mesenchymal cell types: fibroblast, mesothelial cells, endothelial cells, adipocytes myoblasts, chondroblasts, osteoblasts

- Mesenchymal tissue in the skin:
  - Dermis
  - Subcutis

Mesenchymal Tumors

Characteristics



Often referred to as **soft tissue** or **connective tissue** tumors

Most common malignant neoplasia in cats

Benign tumors = -oma

Malignant tumors = -sarcoma

Mixed mesenchymal/epithelial = carcinosarcoma

Mesenchymal Tumors

Adipose tumors
- **Lipoma/sarcoma**

Connective tissue tumors
- **Fibroma/fibrosarcoma**
- **Hemangiopericytoma**
- **Sarcoid**
- **Myxoma/sarcoma**

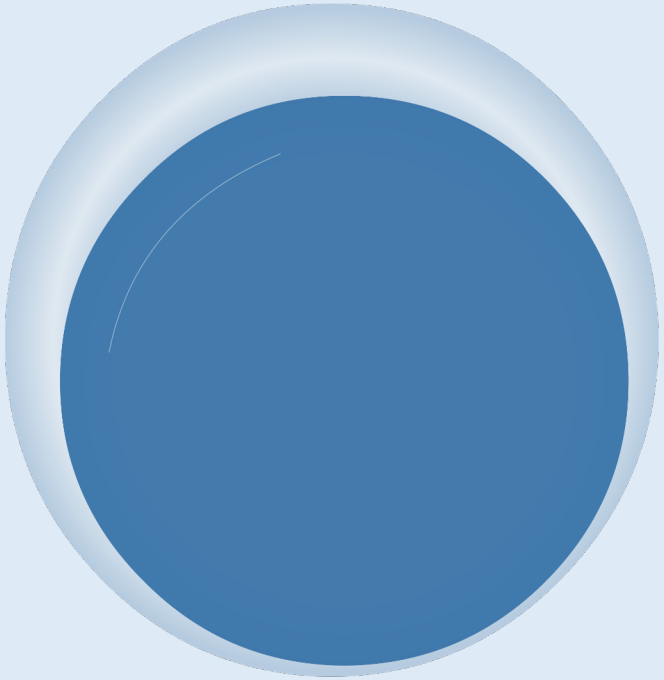
Blood and lymphatic vessel tumors
- **Hemangioma/sarcoma**
- **Glomus tumors**
- **Lymphangioma/sarcoma**

Muscle tumors
- **Leiomyoma/sarcoma**
- **Rhabdomyoma/sarcoma**

Peripheral nerve tumors

Round Cells

Characteristics



- Hematopoietic origin: mast cell, histiocyte, plasma cell, lymphocyte
- TVT? (histiocytic?)

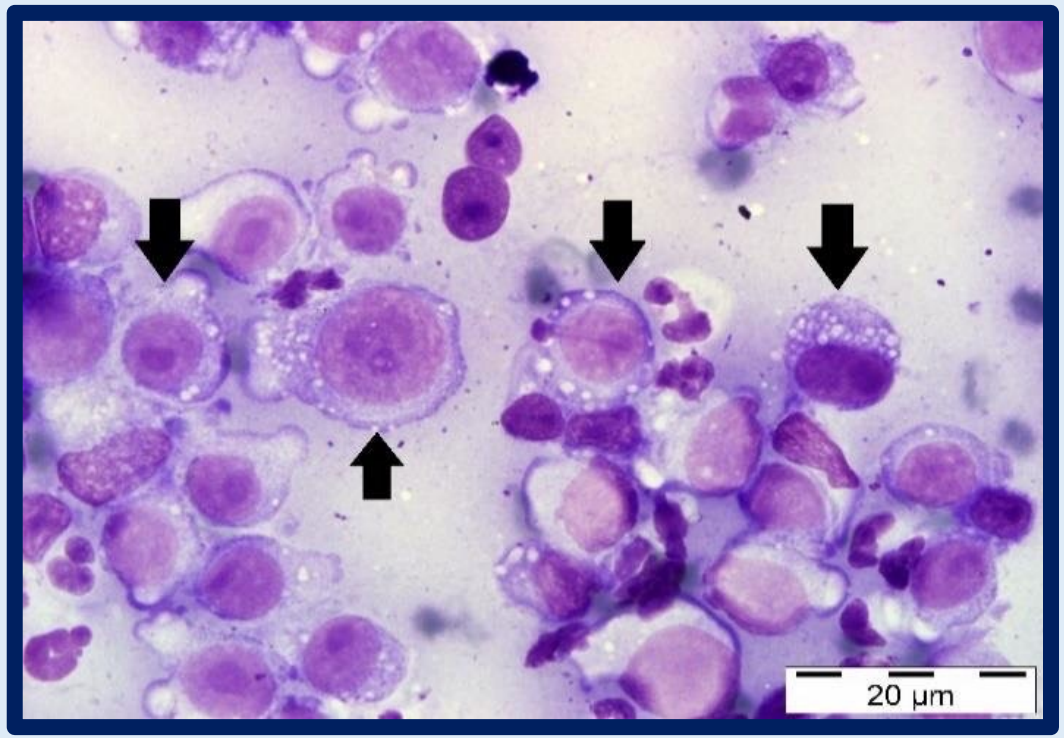
Major round cell types:

- histiocytes
- lymphocytes
- plasma cells
- mast cells
- transmissible venereal tumor cells
- (melanocytes)

- Round cells in the skin:
  - Usually dermis

Round Cell Tumors

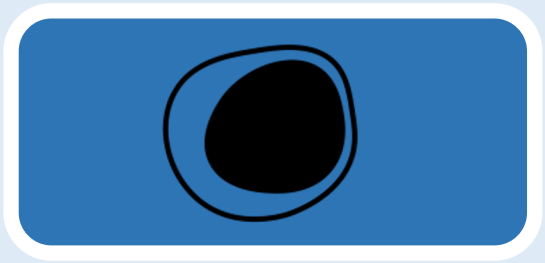
Characteristics



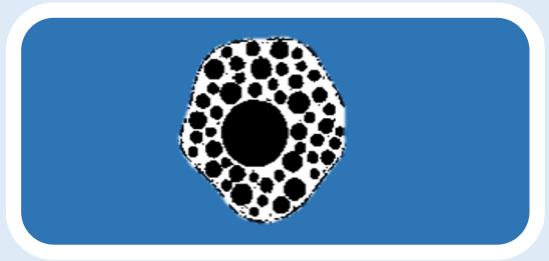
Benign tumors = -oma

Malignant tumors = variable

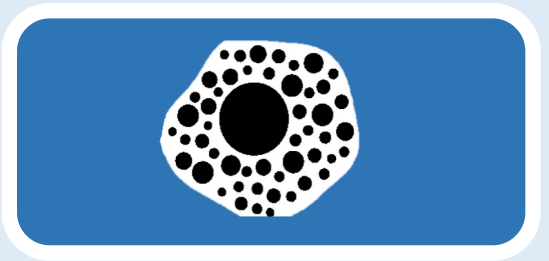
Round Cell Tumors



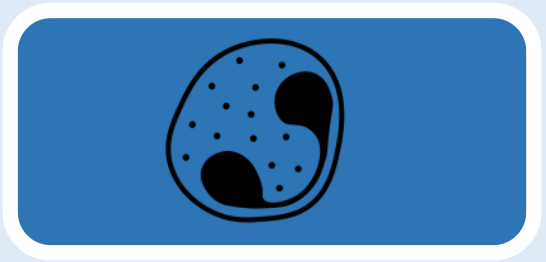
Lymphoma



Mast cell tumors

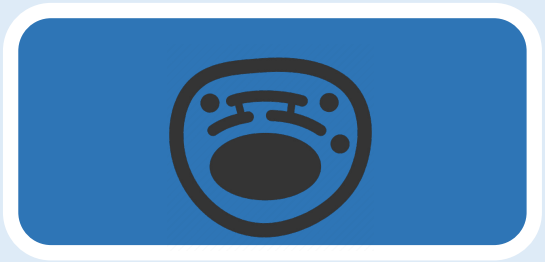


Transmissible venereal tumor



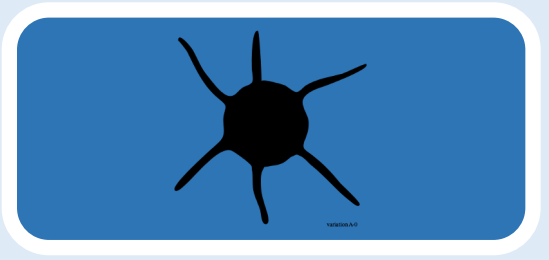
Histiocytic tumors

- **Histiocytoma**
- **Histiocytic sarcoma**
- **Histiocytosis**



Plasma cell tumors

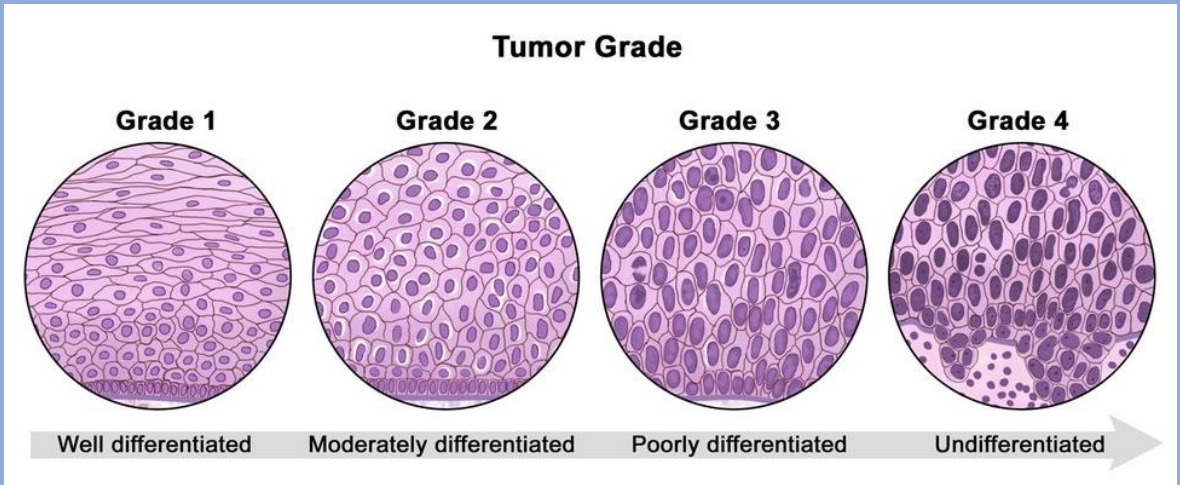
- **Plasmacytoma**
- **Myeloma**
- **Plasmacytosis**



Melanoma

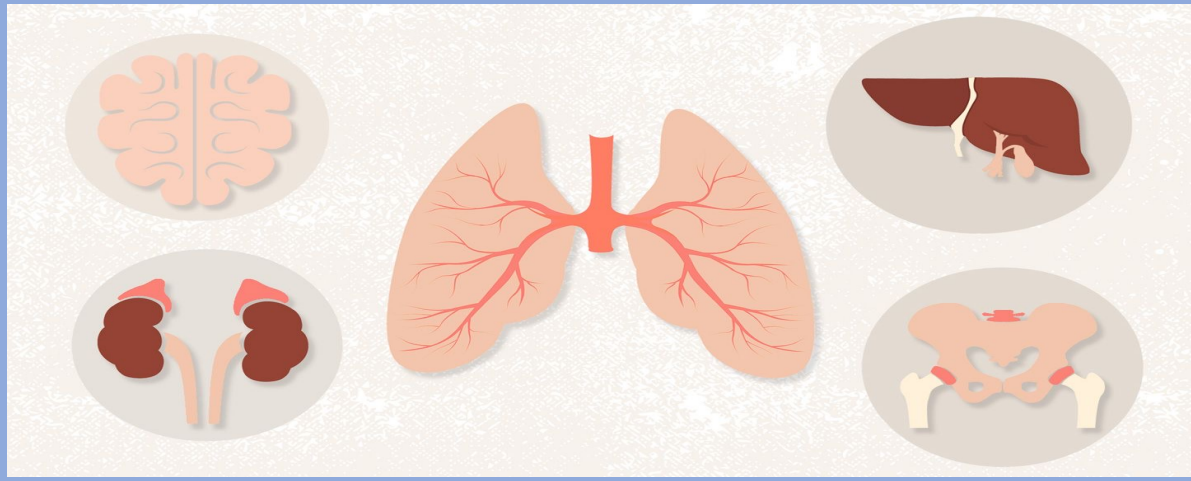
Tumor Grade vs. Stage

Tumor Grade



- Based on microscopic characteristics
- Descriptive (high/low) or numeric designation
- May correspond with tumor behavior, metastasis, and/or potential for recurrence

Tumor Stage



- Extent of spread throughout the body
- Staging – act of performing diagnostic tests to determine stage
- Monitors change from baseline, rate of change, and response to treatment.

Diagnostic Testing

Physical Exam

- Tumor color, size, shape, location, ulceration, consistency (firm, soft)
- Peripheral lymph nodes

Detailed History

- Duration
- Rate of growth
- Other tumors
- Systemic signs
- Therapy

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

Cytology of Skin Tumors

Three categories

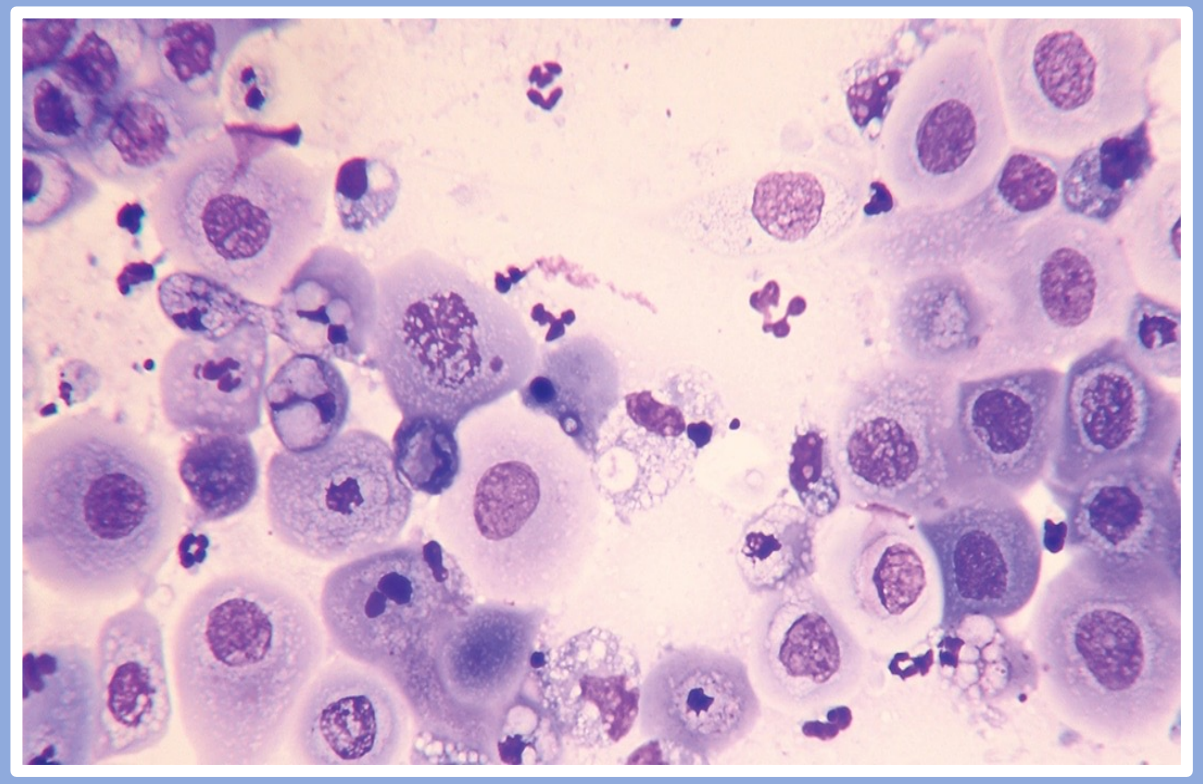
Epithelial tumors

Mesenchymal tumors

Round cell tumors

Epithelial Tumors

Characteristics



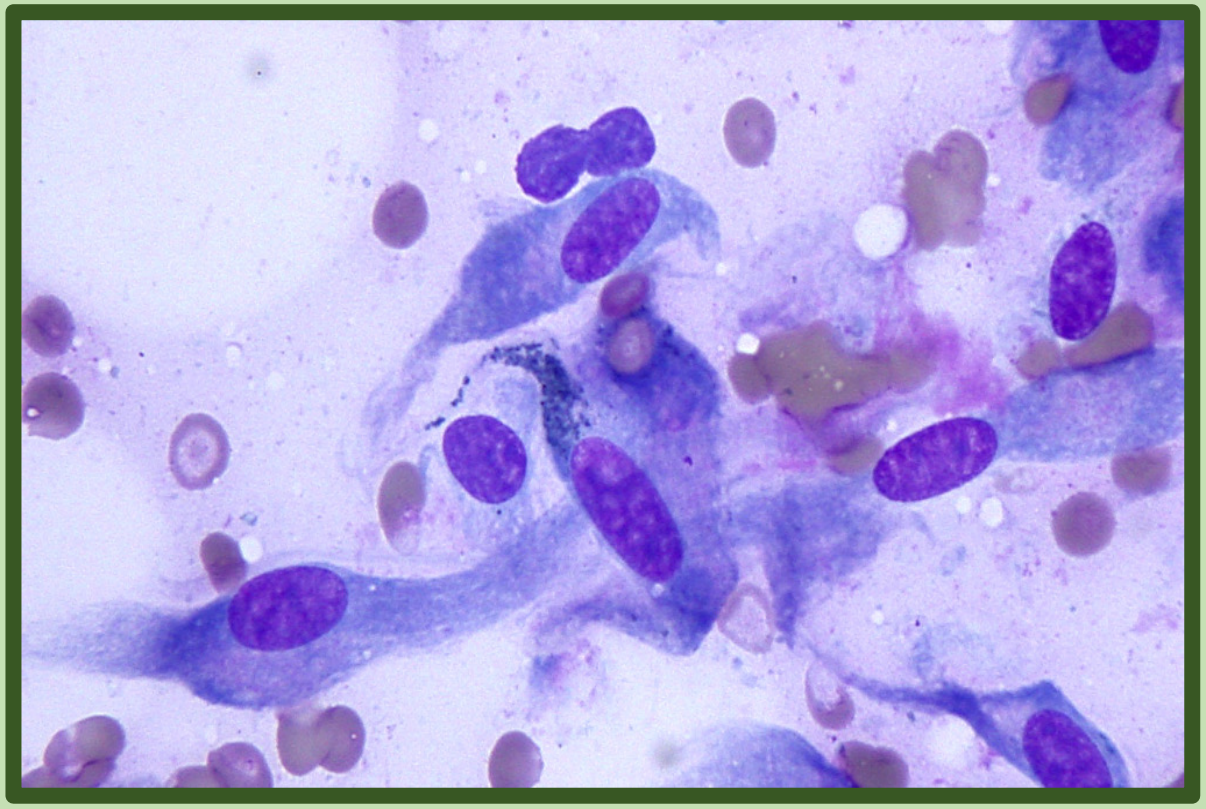
Cell morphology:
- Round, cuboidal, columnar, or polygonal
- Distinct cytoplasmic borders
- Cytoplasmic vacuoles (glands)

Cell grouping:
- Cohesive sheets/clusters (intercellular junctions)
- Poorly differentiated tumors may lose junctions

Degree of exfoliation:
Good

Mesenchymal Tumors

Characteristics



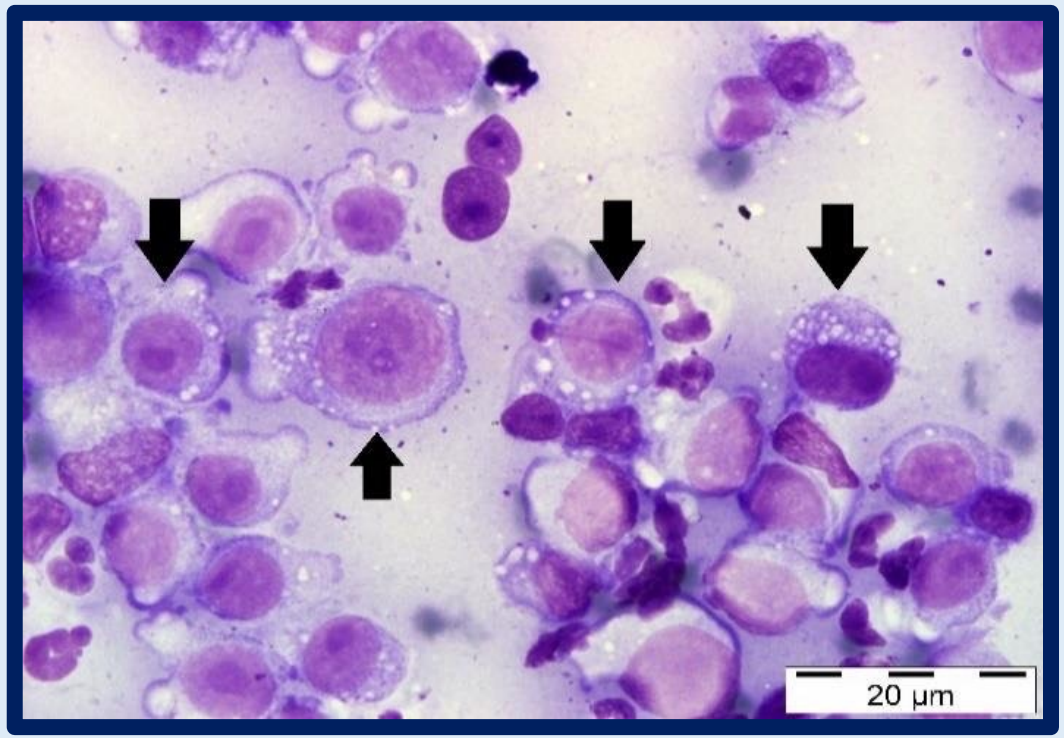
Cell morphology:
- **Spindeloid, stellate, or oval**
- **Cytoplasmic margins indistinct**
- **Often in extracellular matrix**

Cell grouping:
- **Individual or non-cohesive aggregates (no intercellular junctions)**

Degree of exfoliation:
Poor

Round Cell Tumors

Characteristics



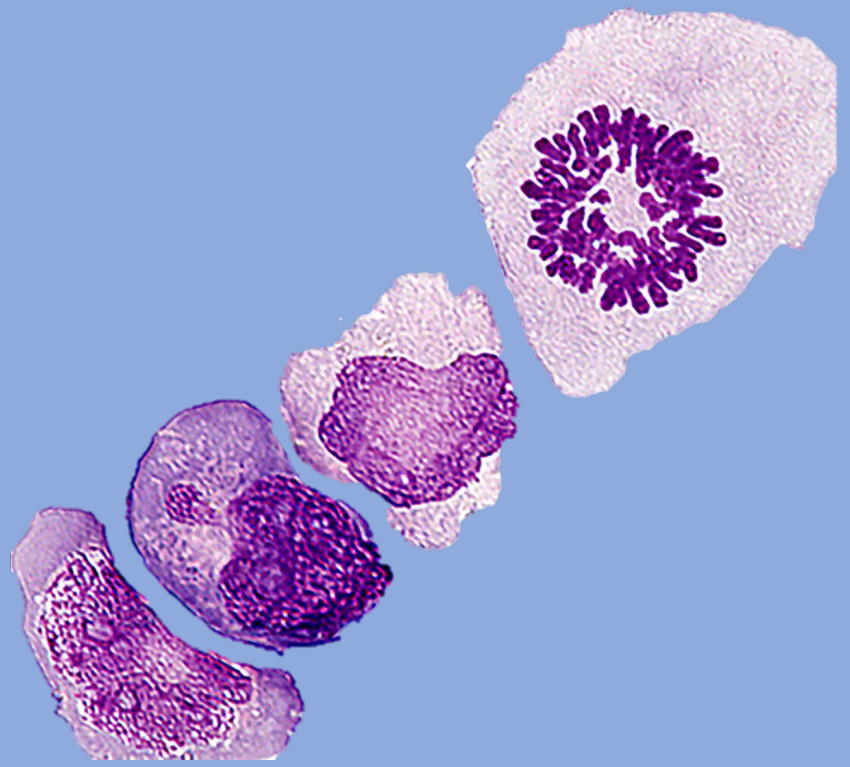
Cell morphology: Round

Cell grouping:
- **Individual in monolayer (no intercellular junctions)**

Degree of exfoliation: Excellent

Criteria of Malignancy

Goal: To distinguish benign from malignant tumors by assessing variation

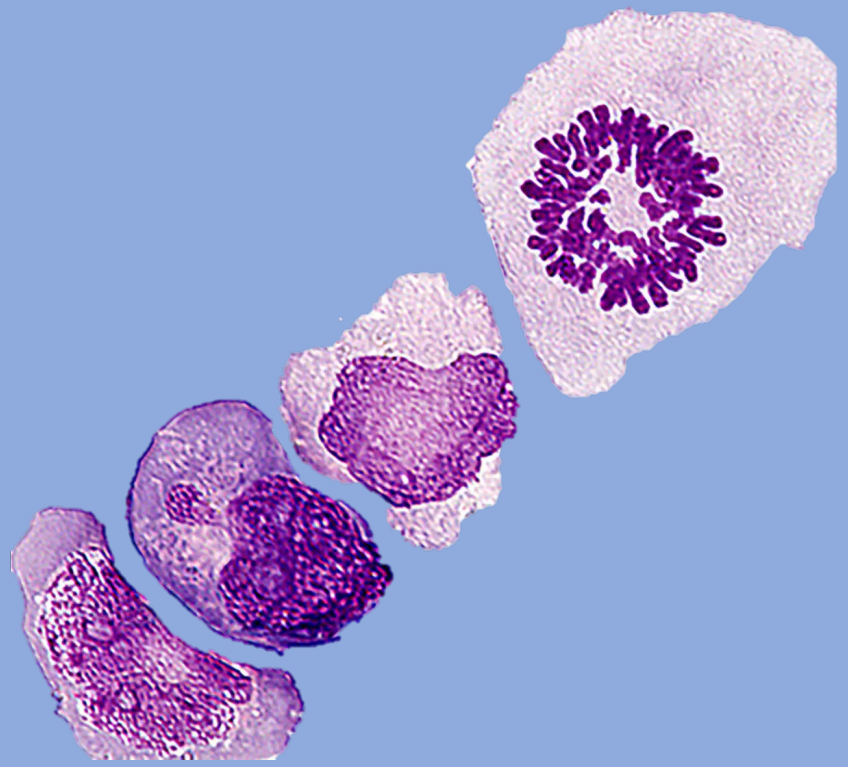


More malignant
= less differentiated
= more variation in cell morphology

More benign
= more uniform cell size and NC ratio, resemble cell of origin

Criteria of Malignancy

Characteristics



Nuclear Alterations:

1. Size
2. Shape
3. Position
4. Number
5. Nucleoli
6. Mitoses
7. Nuclear : cytoplasmic ratio
8. Chromatin pattern

Cytoplasmic Alterations:

1. Relative amount
2. Quality
3. Content

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

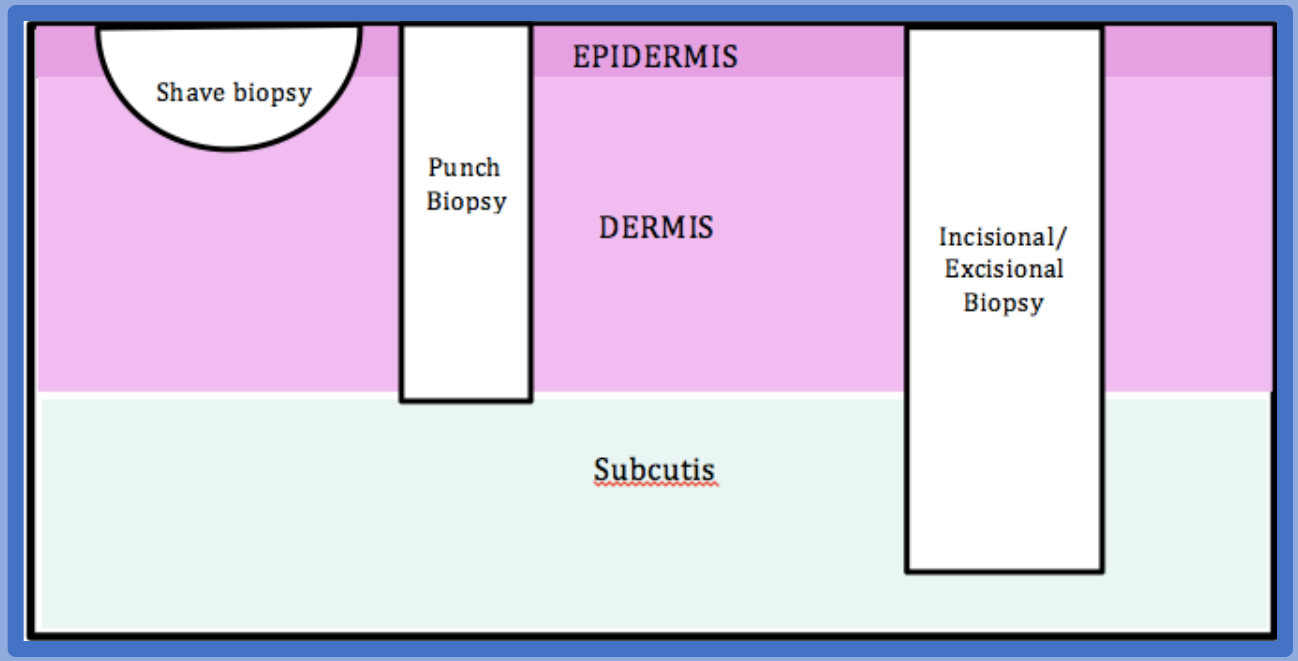
Histopathology

Often required for diagnosis

Removal of tissue from a living organism for microscopic evaluation

Primary purpose: determine diagnosis precisely for proper treatment

Secondary purpose: predict tumor behavior and prognosis



Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

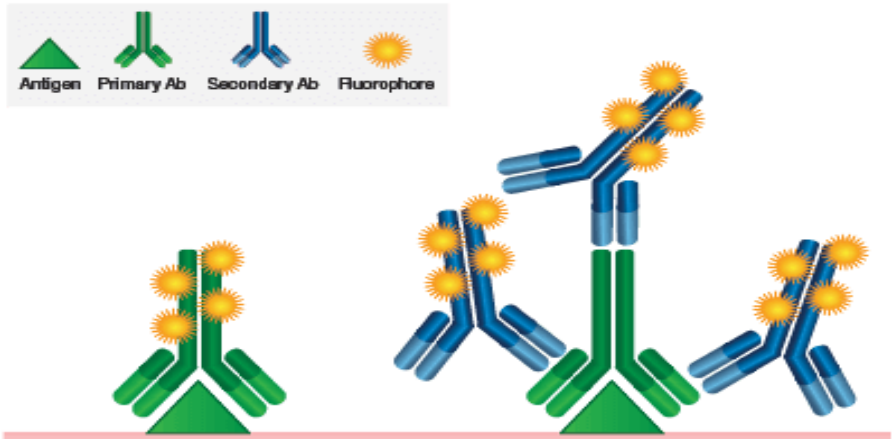
Imaging

Molecular Genetics

Node Evaluation

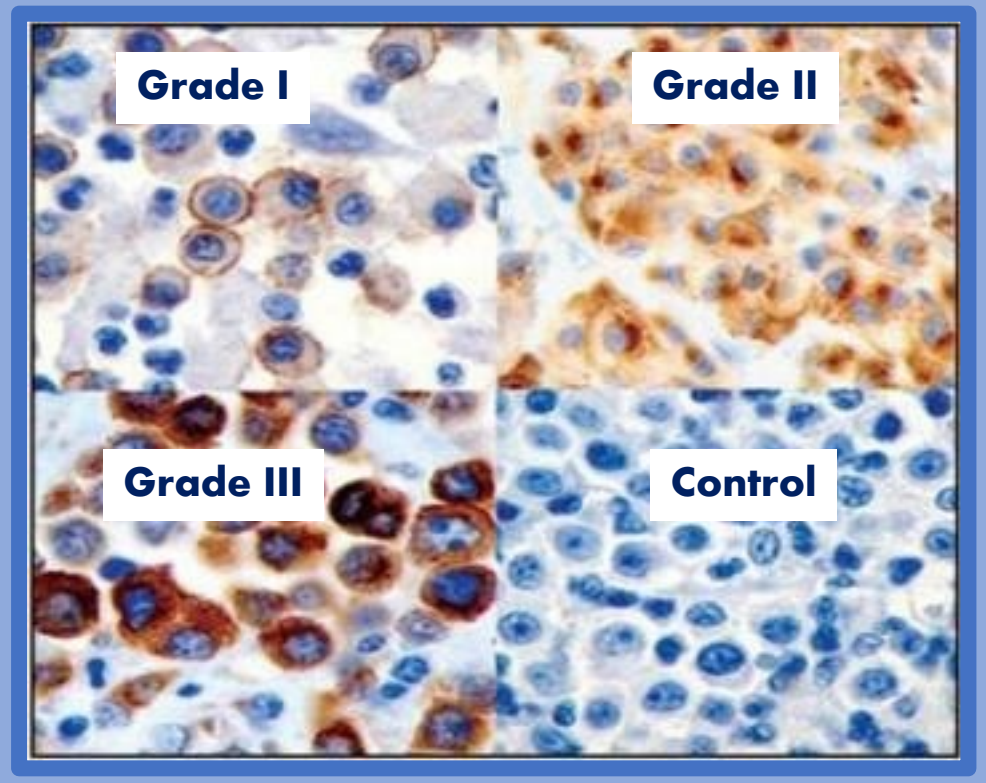
Flow Cytometry

Immunohistochemistry

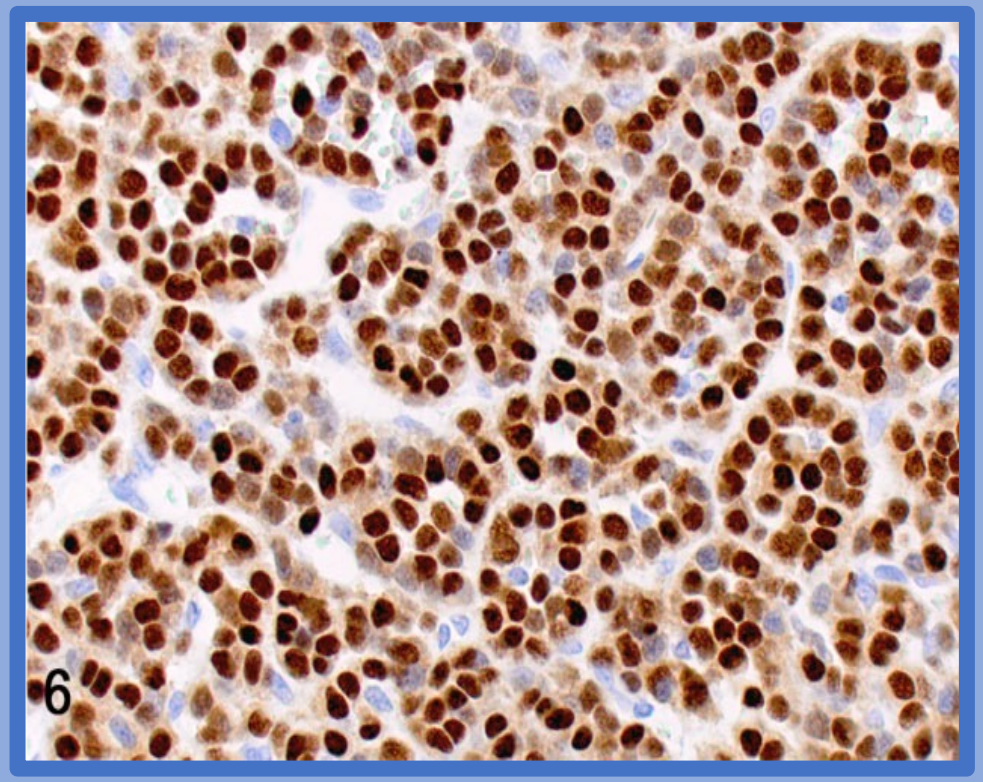


Antigen Detection	Direct immunofluorescence with primary antibody conjugated to a fluorophore	Indirect immunofluorescence with secondary antibody conjugated to a fluorophore
Protocol	Parallel staining	Parallel staining
Primary Antibody	Same host species can be used for multiple targets	Different host species or isotype for each target
Seconday Antibody	No	Yes
Signal Amplification	None	Moderate

Immunohistochemistry



Mast Cell Tumor
c-kit staining



Plasma Cell Tumor
MUM-1/IRF4 staining

Immunohistochemistry

Tumor Type	IHC Marker
Carcinoma (epithelial)	Cytokeratin
Hemangiosarcoma (endothelial)	Factor VIII related antigen, Claudin 5, CD31
Histiocytoma	CD18, CD204, iBA-1
Lymphoma - B-cell	CD79a, CD20, PAX5
Lymphoma - T-cell	CD3
Mast cell tumor	CD117/c-kit
Melanoma	Melan-A, PNL2, TRP-1, TRP-2, +/- S100
Muscle tumor - smooth	Smooth muscle actin, desmin
Muscle tumor - skeletal	Myogenin D, sarcomeric actin, desmin
Neuroendocrine tumor	Chromogranin A, synaptophysin
Plasma cell tumor	MUM-1
Sarcoma (mesenchymal)	Vimentin

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

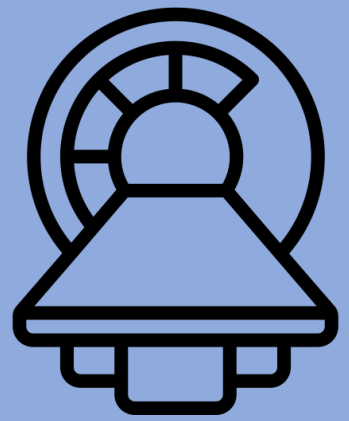
Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

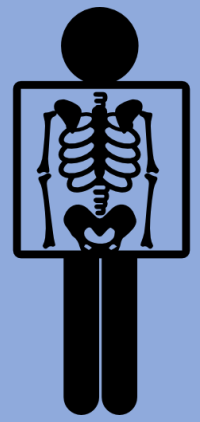
Diagnostic Imaging



MRI

PET

CT



Radiographs

US

Nuclear Scintigraphy

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

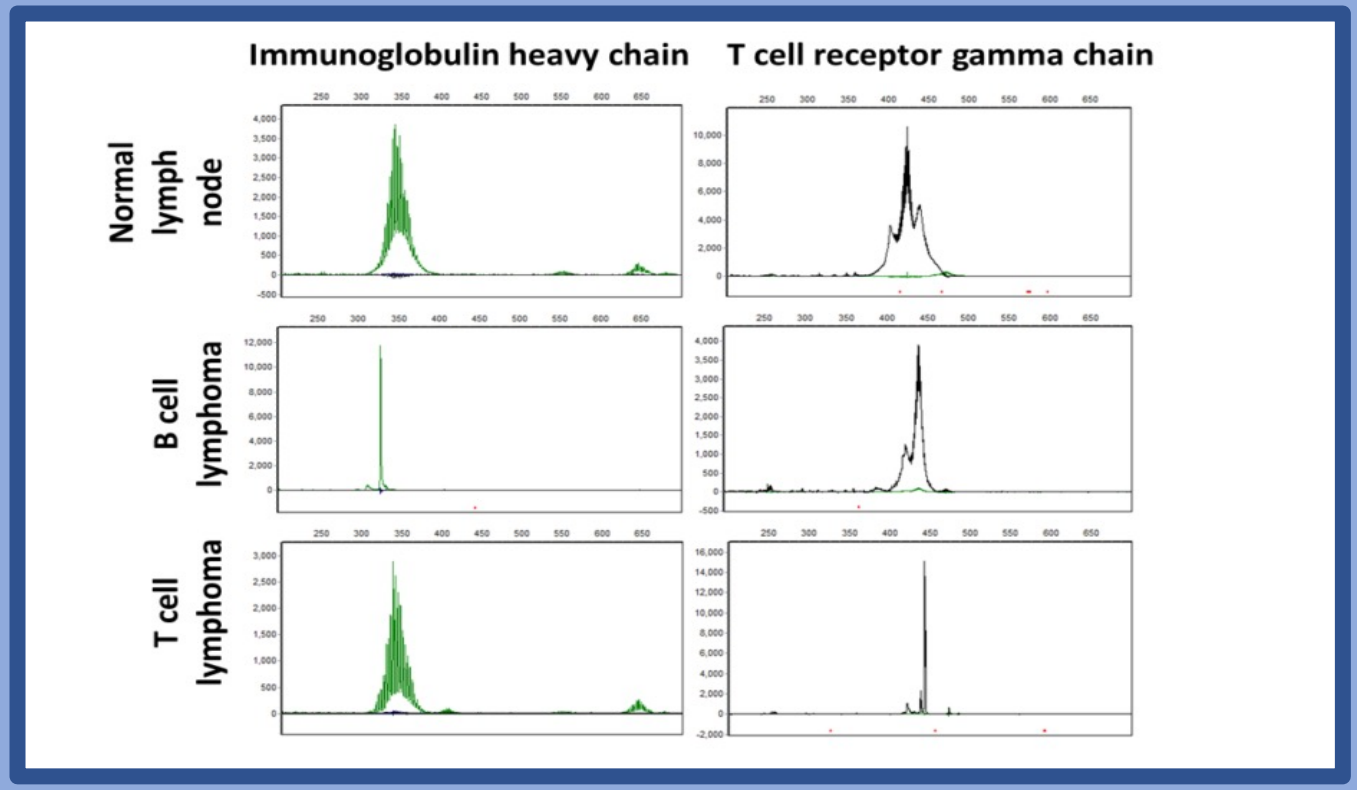
Molecular Genetics

Analysis of genes and gene expression

Molecular Genetics

PCR Amplification of Antibody Receptor Genes (PARR) Testing

- Reactive vs. neoplastic
- Establish prognosis
- Guide treatment



Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

Imaging

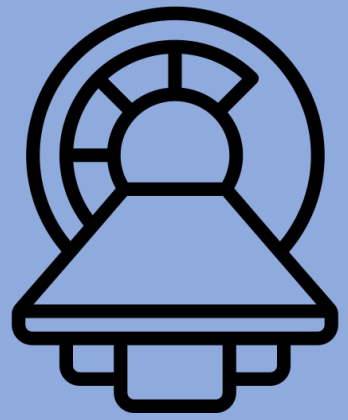
Molecular Genetics

Node Evaluation

Flow Cytometry

Lymph Node Evaluation

Fine needle aspirate



MRI

PET

CT

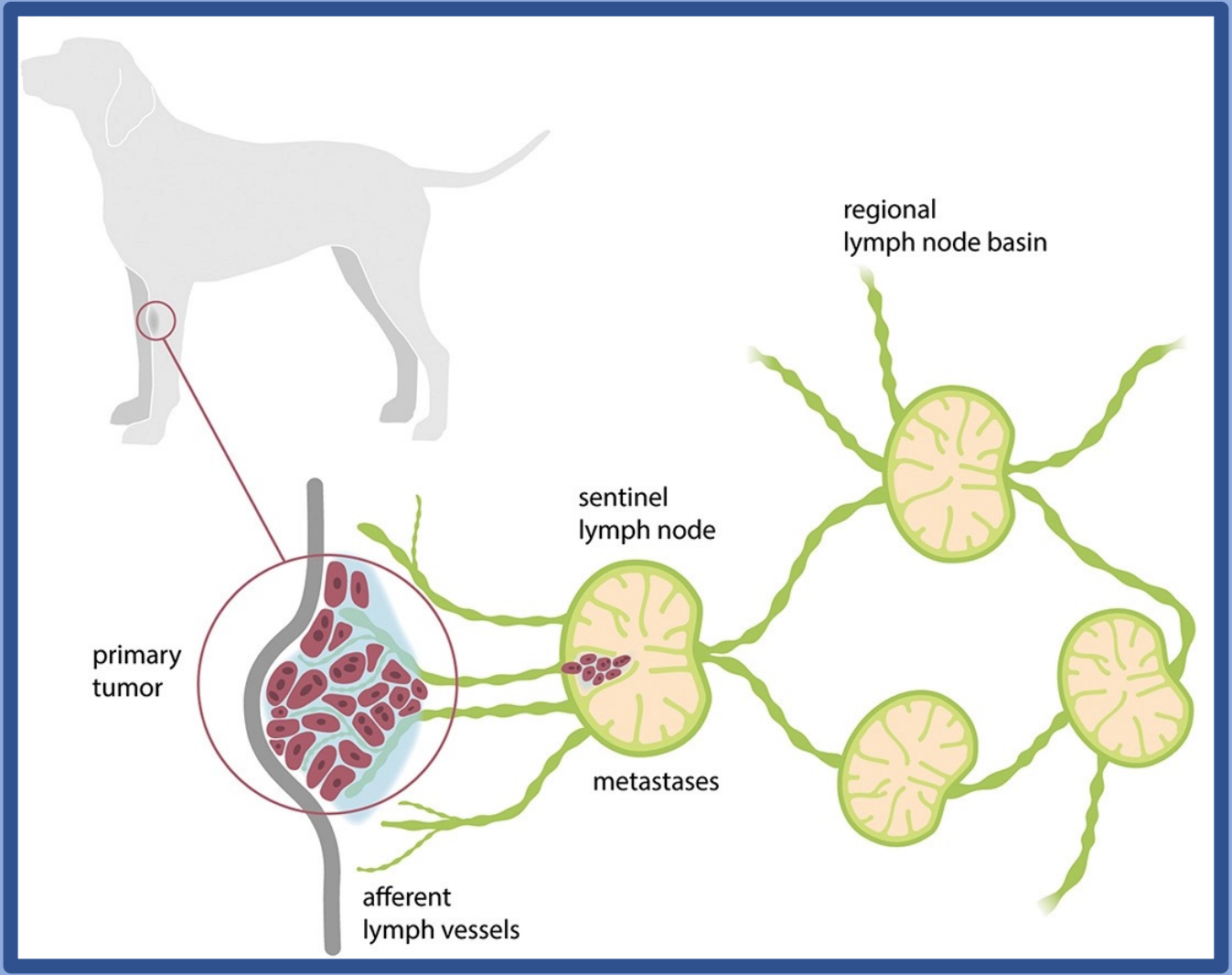
Histopathology

Lymphangiography

US

Lymphoscintigraphy

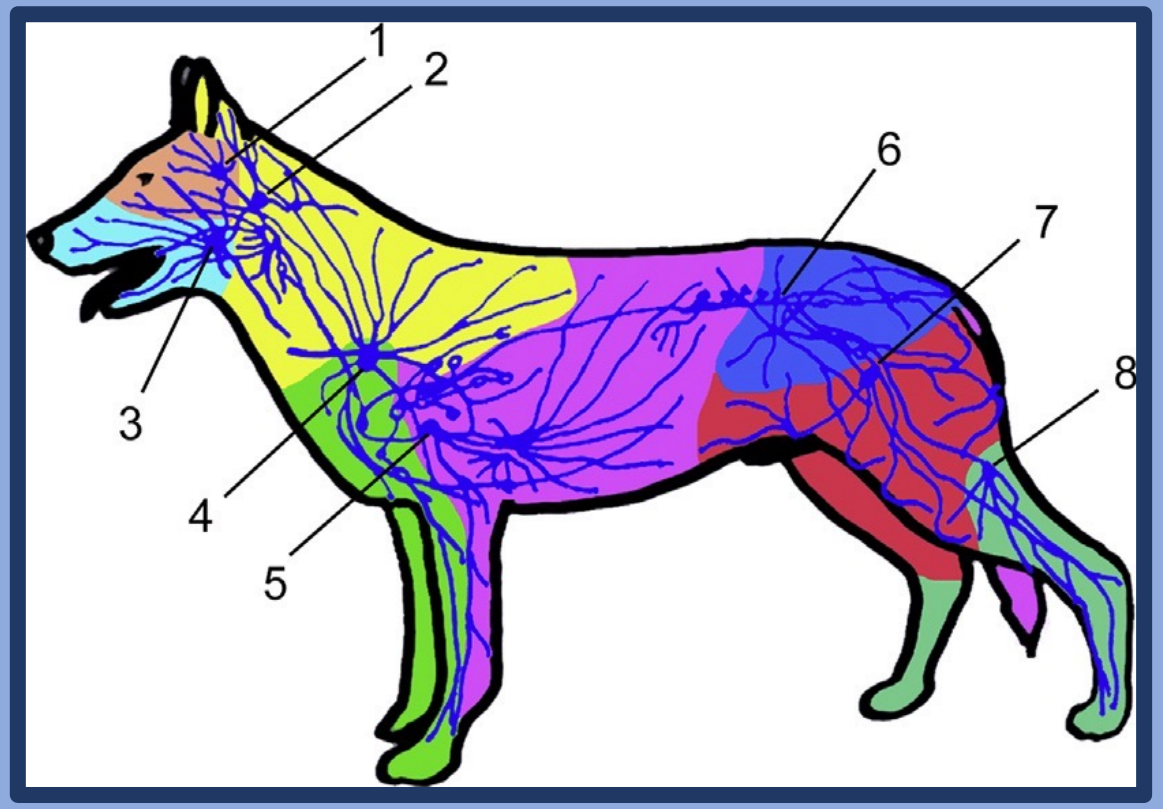
Lymph Node Evaluation



Sentinel lymph node:

the first lymph node to which cancer cells are most likely to spread from a primary tumor

Lymph Node Evaluation



Lymphatic drainage patterns:

Determine appropriate node to aspirate during staging

1. **Parotid**; 2. **Submandibular**; 3. **Retropharyngeal**;
4. **Prescapular**; 5: **Axillary**; 6. **Iliac**; 7: **Inguinal**; 8. **Popliteal**

Diagnostic Testing

Cytology

Histopathology

Immunohistochemistry

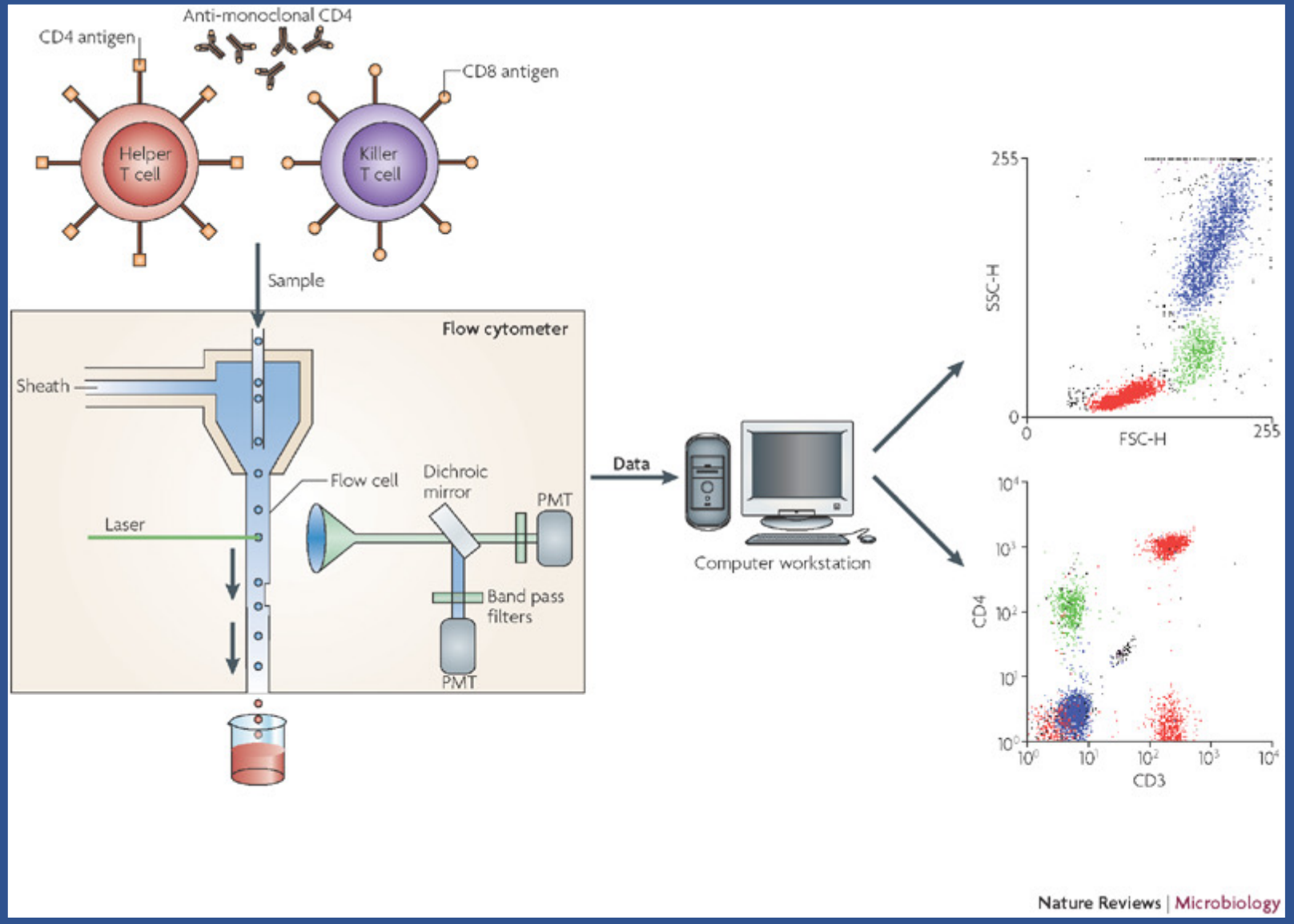
Imaging

Molecular Genetics

Node Evaluation

Flow Cytometry

Flow Cytometry



Tumor Treatments

4 Types in Dogs and Cats

- Ablative Therapy
- Cytotoxic Therapy
- Biologic Therapy
- Supportive Care

Tumor Treatments

Biologic Therapy

Cause immune system to specifically recognize and destroy tumor cells

- **Immunotherapy**
- **Vaccines**
- **Cytokine therapy**
- **Gene therapy**

Supportive Care

- **Pain / pruritus control**
- **E-collar / protective clothing**
- **Secondary infection treatment**
- **Nutritional support**
- **Symptom relief – paraneoplastic syndromes**

Ablative Therapies

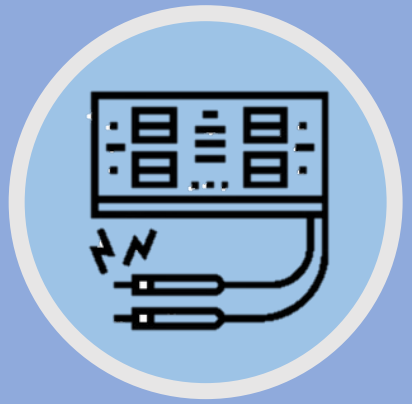
Surgery

Laser Ablation

Hyperthermia

Cryotherapy

Electrosurgery



Vascular or Tumor Ligation

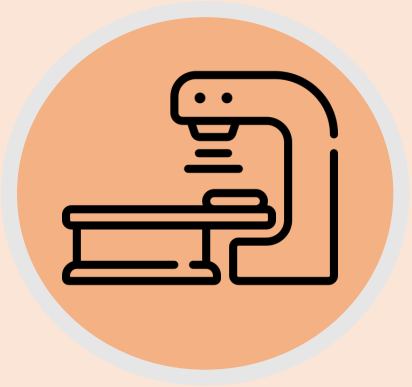
Cytotoxic Therapies

Uses: curative, palliative, or part of adjuvant protocol

Chemotherapy

Photodynamic Therapy

Radiation Therapy



Electrochemotherapy

Cytotoxic Therapies

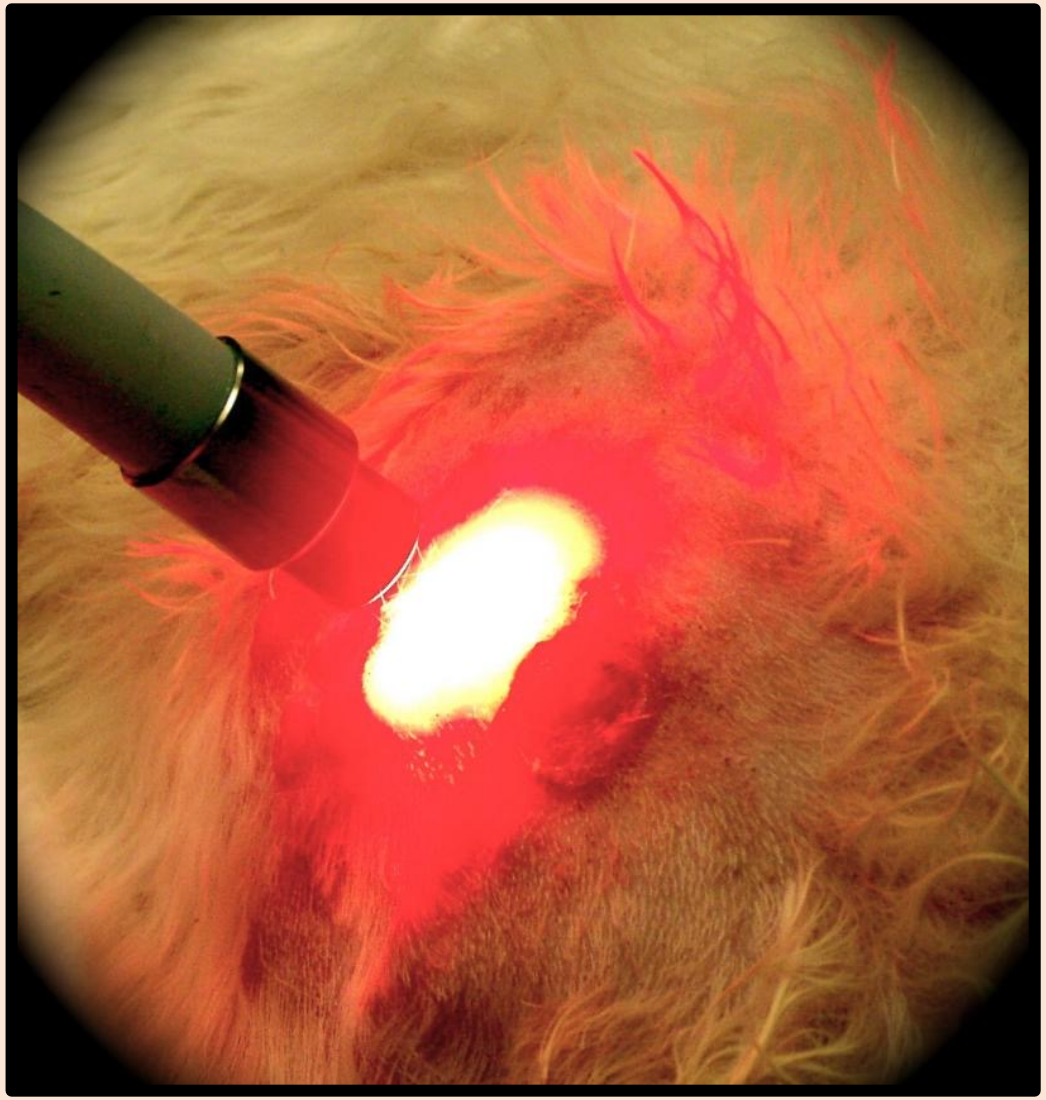
Photodynamic Therapy

- **Use of light of specific, activating wavelengths, plus molecular oxygen and a photosensitizer that accumulates in a tumor.**
- **Photosensitizer reacts with molecular oxygen to create reactive oxygen species**
- **Effects:**
  1. **Vascular stasis and necrosis**
  2. **Membrane damage**
  3. **Apoptosis**
  4. **Inflammatory cascades**

https://doi.org/10.3390/app122312276

Cytotoxic Therapies

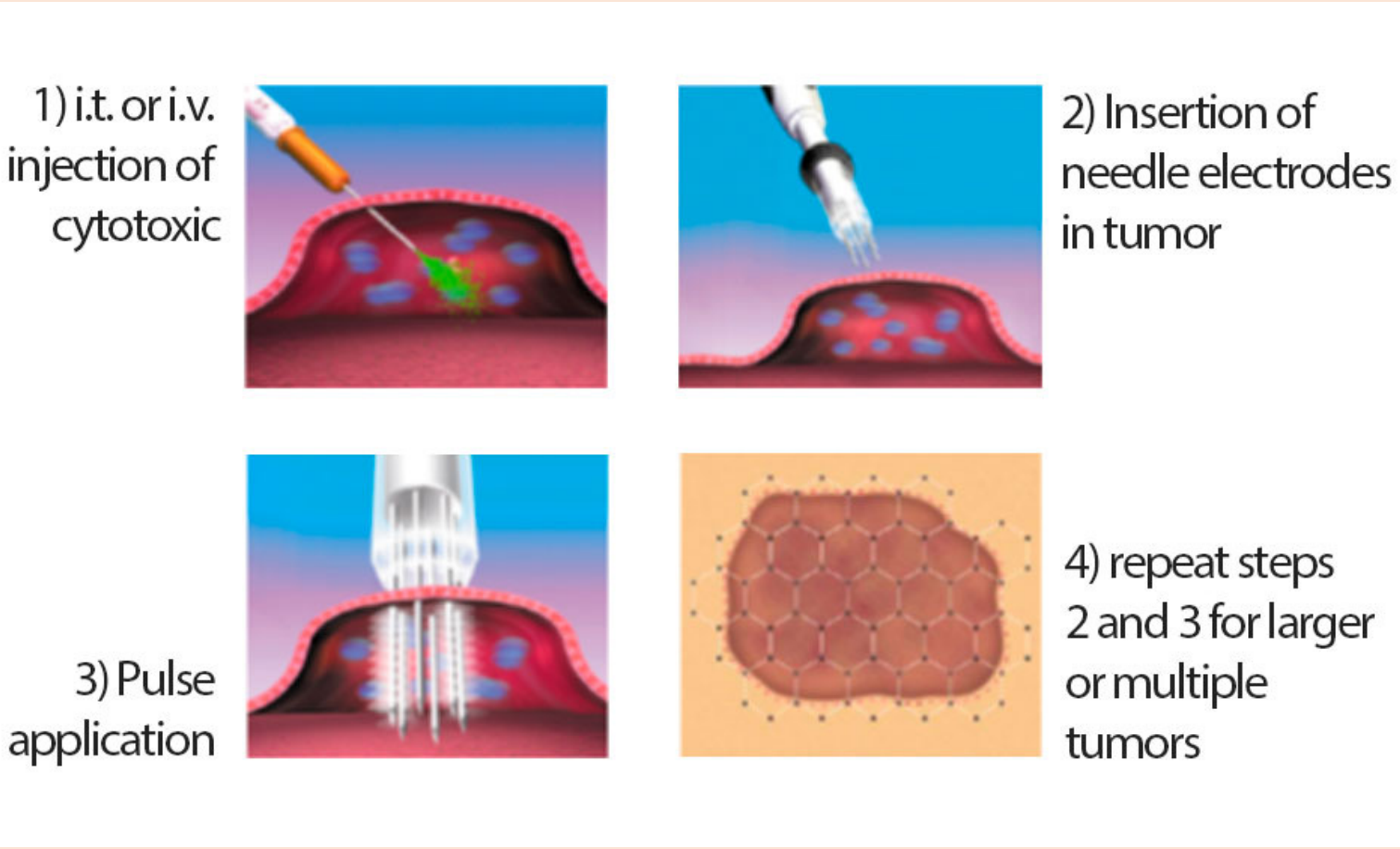
Photodynamic Therapy



http://northcoastvetspecialist.com/photodynamic_therapy

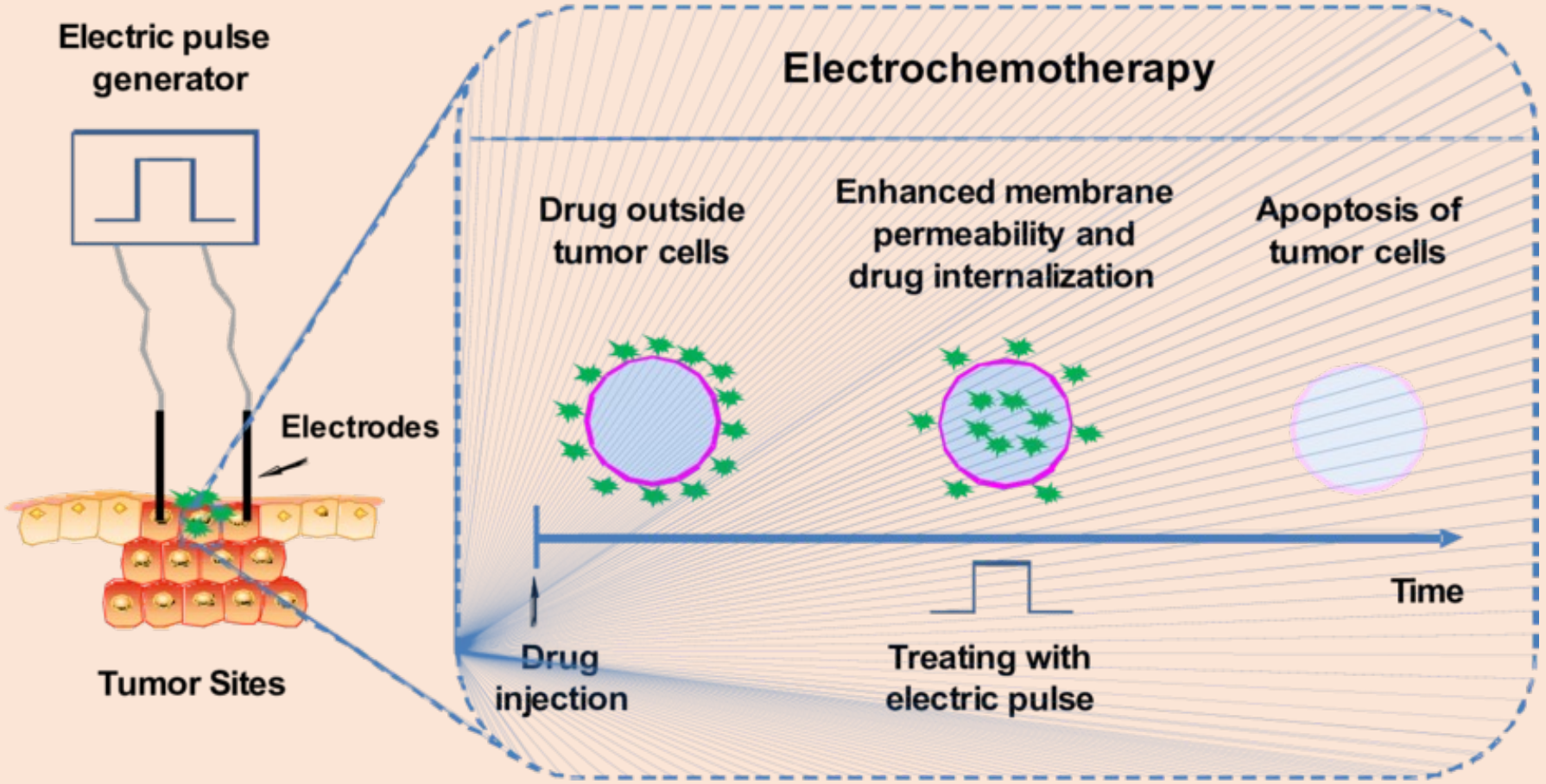
Cytotoxic Therapies

Electrochemotherapy



Cytotoxic Therapies

Electrochemotherapy



Cytotoxic Therapies

Electrochemotherapy

- **Electrical pulses cause reversible permeabilization of cell membranes to enable entry of chemotherapeutic drugs or immunotherapies into cells (electroporation)**
- **Incompletely excised cutaneous and SQ tumors**
- **3 effects:**
  1. **Directly cytotoxic**
  2. **Antivascular**
  3. **Immunological**

Cytotoxic Therapies

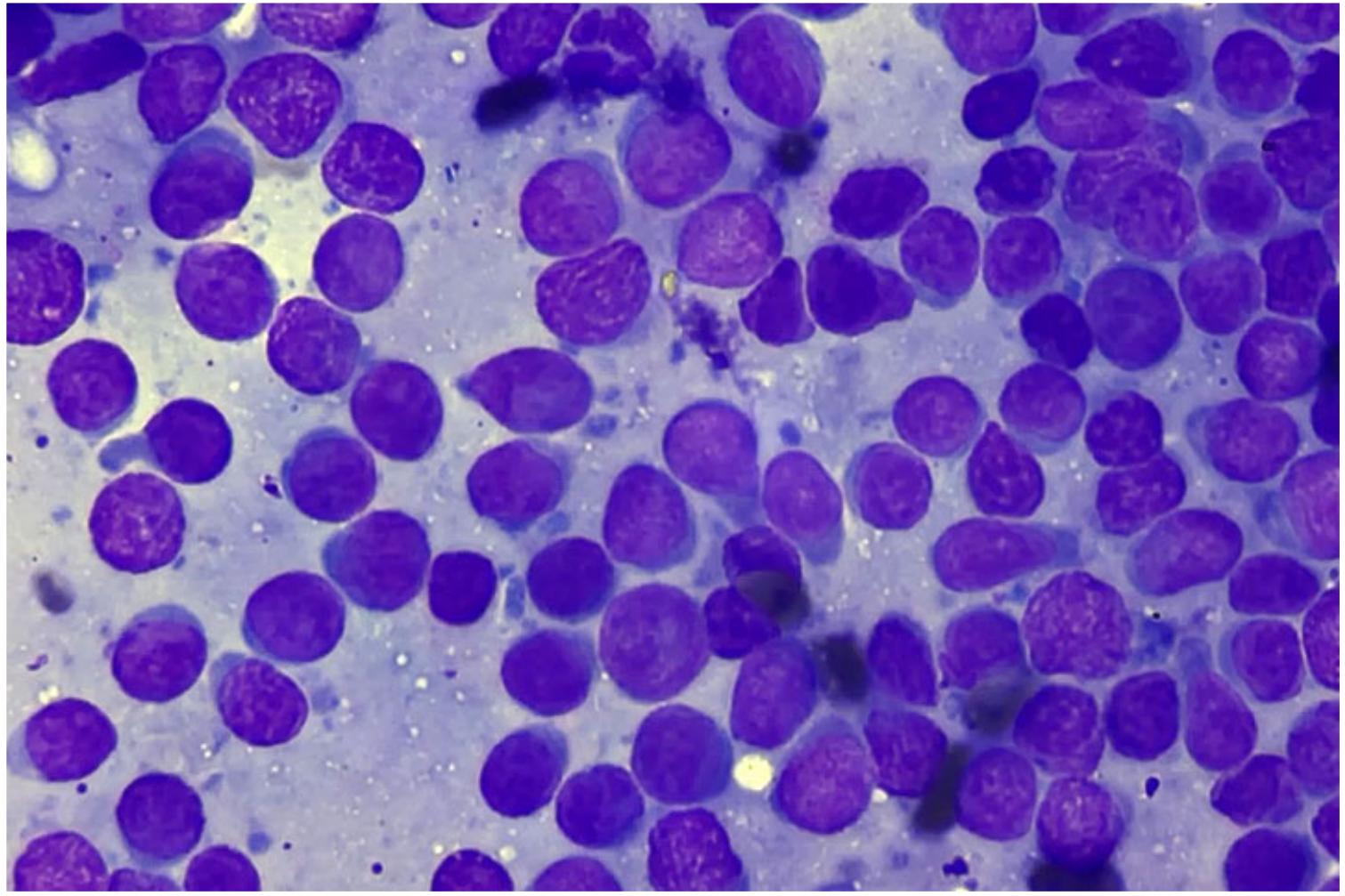
Electrochemotherapy

Median Survival Time

The length of time from either the date of diagnosis or the start of treatment that half of the patients with the disease are still alive.

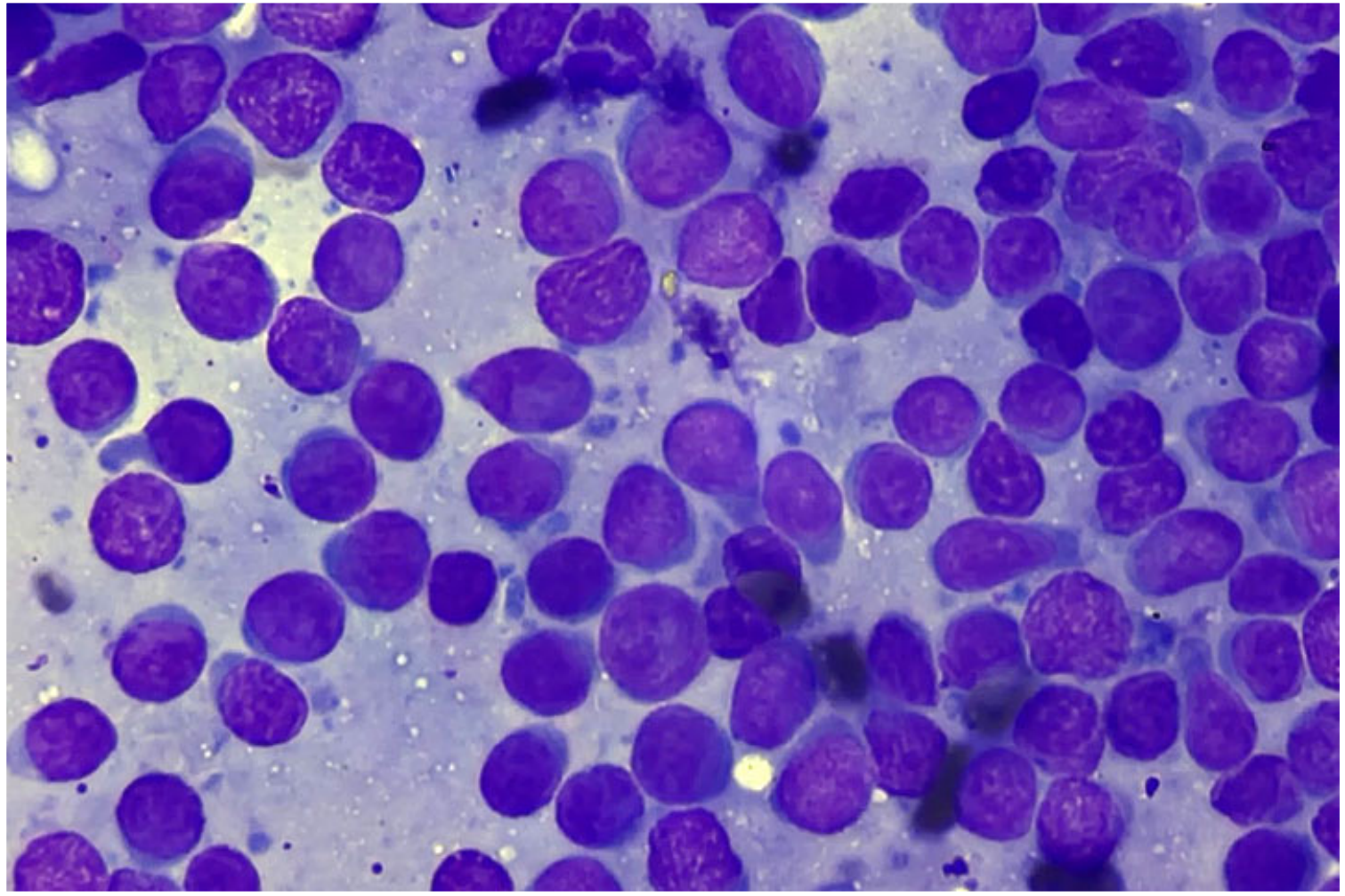
Case 1

Cytology



Diagnosis?

Cytology



Lymphocytes

Cutaneous Lymphoproliferative Disorders

5 Types in Dogs and Cats

- Cutaneous Lymphoma
- Cutaneous Lymphocytosis
- Tympanic Bulla Lymphoma
- Lymphomatoid Granulomatosis
- Lymphoid Hyperplasia

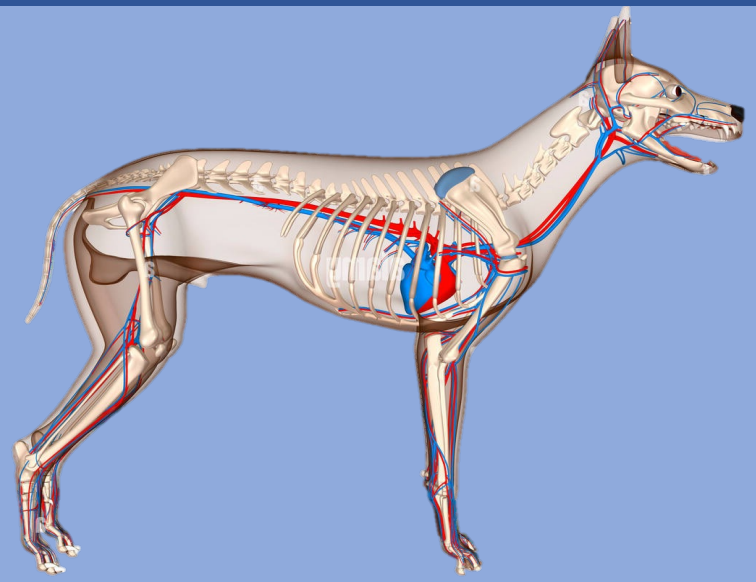
Cutaneous Lymphoma

2 Types in Dogs and Cats

Epitheliotropic

Non-epitheliotropic

Cutaneous Lymphoma



- **Etiology:** Unknown
  - Chronic inflammation?
  - FeLV (cats)?
- **Pathogenesis:** Both types most commonly T-cell origin
  - B-cell origin rarer and more likely to be non-epitheliotropic

Cutaneous Lymphoma

Diagnostic Evaluation

Cytology

Histopathology

IHC

PARR

Flow Cytometry

Staging

Cutaneous Lymphoma

Cytology

Numerous lymphocytes

Limited diagnostic – can't categorize or differentiate the wide spectrum of lymphomas or other lymphocytic conditions

Cutaneous Lymphoma

Histopathology

Pautrier's microabscesses:

Discrete collections of neoplastic lymphocytes in the upper layers of the epidermis (epitheliotropic cutaneous lymphoma)

Cutaneous Lymphoma

Histopathology

Serial biopsies may be needed

Cutaneous Lymphoma

IHC

PARR

Establish type and character of lymphoid infiltrate

- **IHC – establishes infiltrate as lymphocytes and characterizes them**
  - **CD_3 = T-cell**
  - **CD_{20} and CD_{79a} = B-cell**
- **PARR – establishes clonality of lymphocytes and characterizes them based on receptor (B- or T-cell)**

Cutaneous Lymphoma

Flow Cytometry

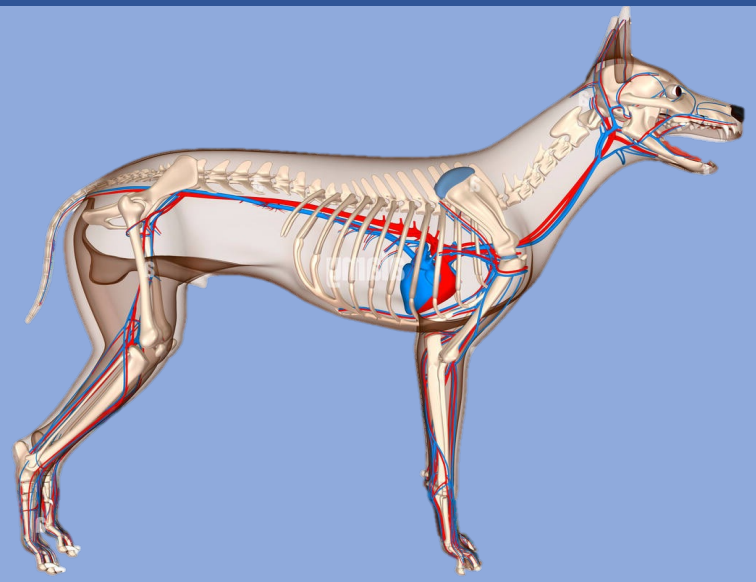
- Another method to establish cells as lymphocytic
  - An option but most commonly used on fluid samples > cytology.

Cutaneous Lymphoma

Staging

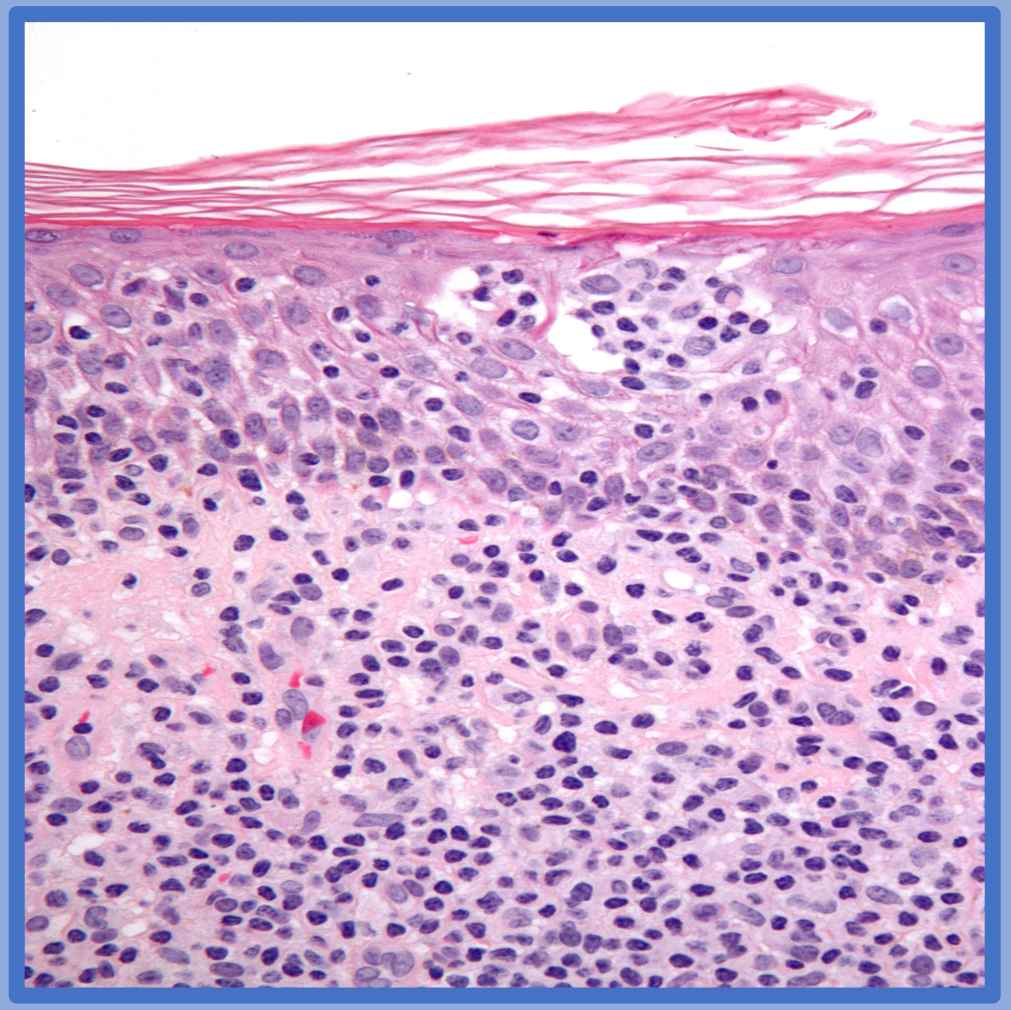
- **Non-epitheliotropic lymphoma - critical**
- **Epitheliotropic lymphoma - disseminated disease rarer**

Cutaneous Lymphoma



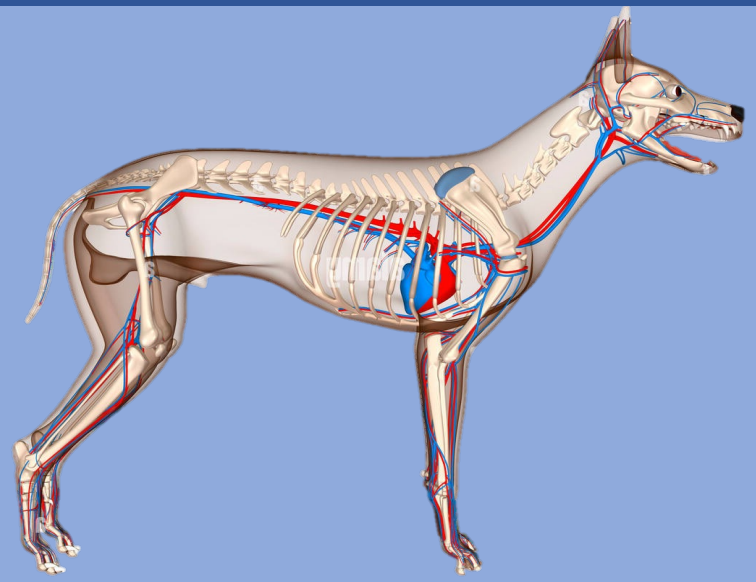
- **<u>Prognosis</u>: Poor**
  - **Inevitably fatal**
  - **Certain subtypes worse**
    - **Tarsal non-epitheliotropic lymphoma – cats**
    - **Neoplastic lymphocytes in blood**
    - **Poor chemotherapeutic response**

Cutaneous Epitheliotropic Lymphoma



- Neoplastic lymphocytes hone to epithelial tissues of the skin
  - Epidermis, hair follicles, glands
- Expression of integrins → direct interactions with keratinocytes

Cutaneous Epitheliotropic Lymphoma

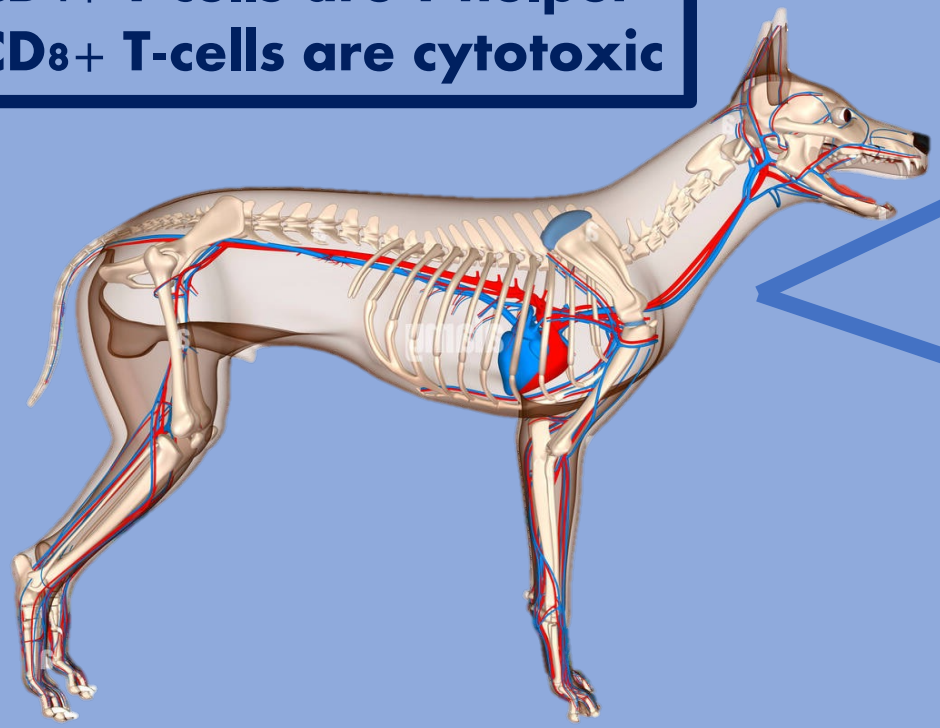


- Most common form of cutaneous lymphoma in dogs
- Less common form of cutaneous lymphoma in cats
- Overall uncommon
  - <1% skin tumors in dogs
  - 0.2-3% skin tumors in cats

Cutaneous Epitheliotropic Lymphoma

Etiology/Signalment

Reminder:
CD_4+ T-cells are T-helper
CD_8+ T-cells are cytotoxic

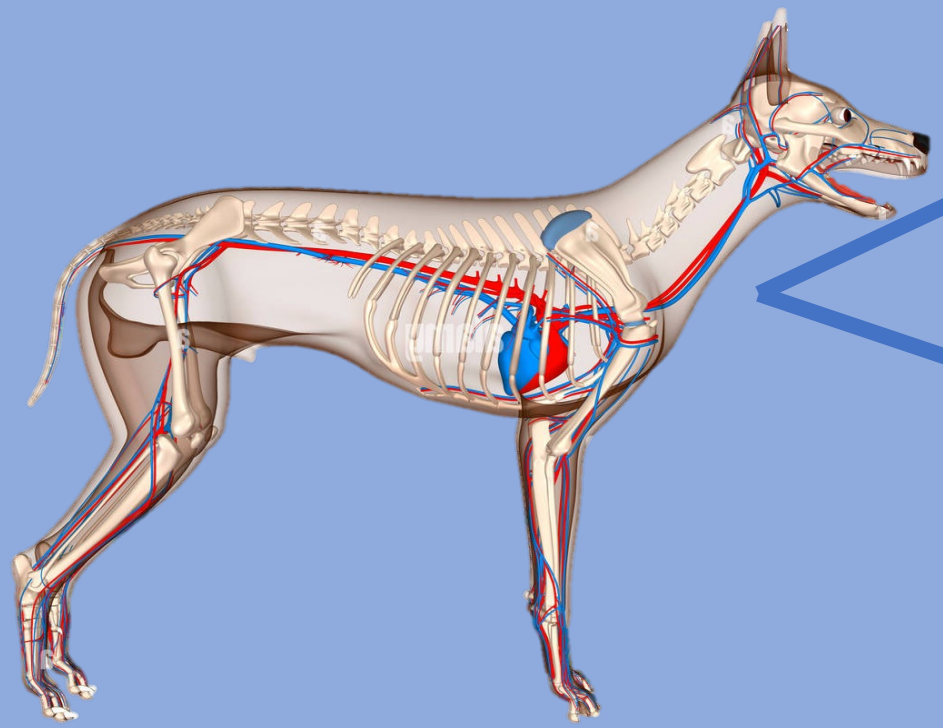


Pathogenesis:

- **Infiltrating lymphocytes are usually T-cells**
  - **80-90% CD_8+**
  - **~60% γ/δ**
  - **Remainder are CD_4- CD_8- T-cells**
- **+/- increased CD_{25}+ T-cells**
- **Increased Th-1 type cytokines IL-12 and IFN-γ in affected skin**
- **Increased CD_8+ T-cell markers in affected skin (perforin, granzyme B)**

Cutaneous Epitheliotropic Lymphoma

Etiology/Signalment

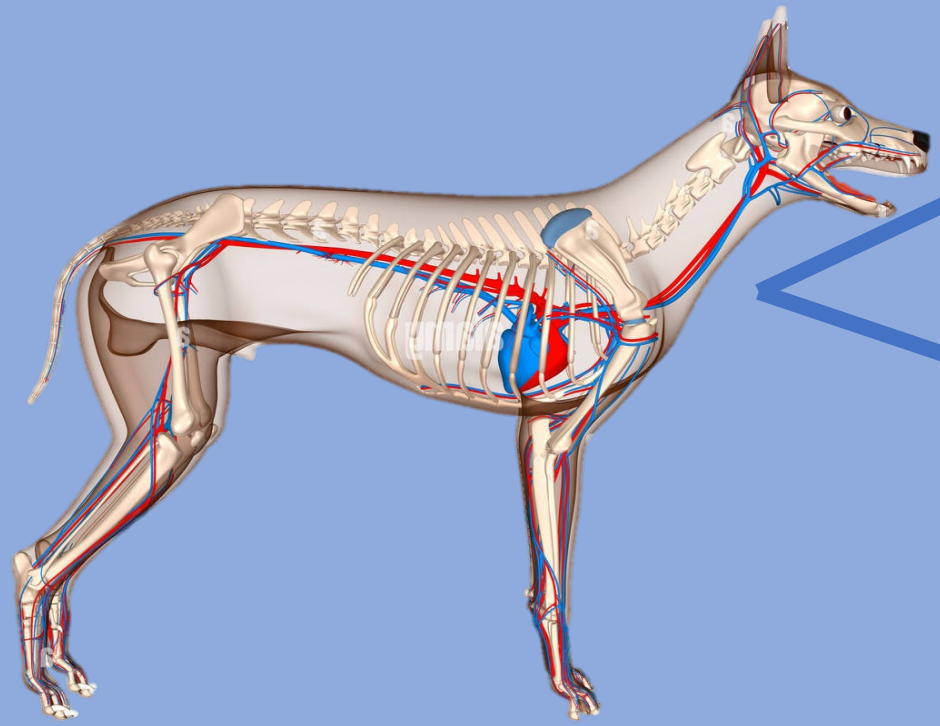


Signalment:

- **Older dogs**
- **Breeds: cocker spaniels, boxers, golden retrievers?**

Cutaneous Epitheliotropic Lymphoma

Clinical Signs

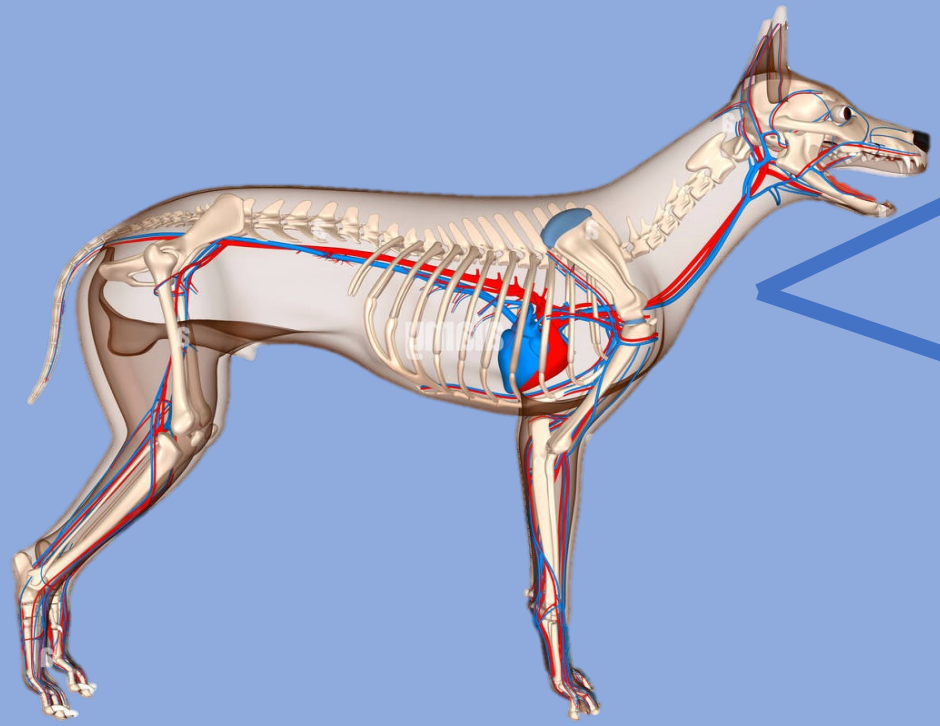


3 clinical forms:

1. Mycosis fungoides
2. Pagetoid reticulosis
3. Sezary syndrome

Cutaneous Epitheliotropic Lymphoma

Clinical Signs

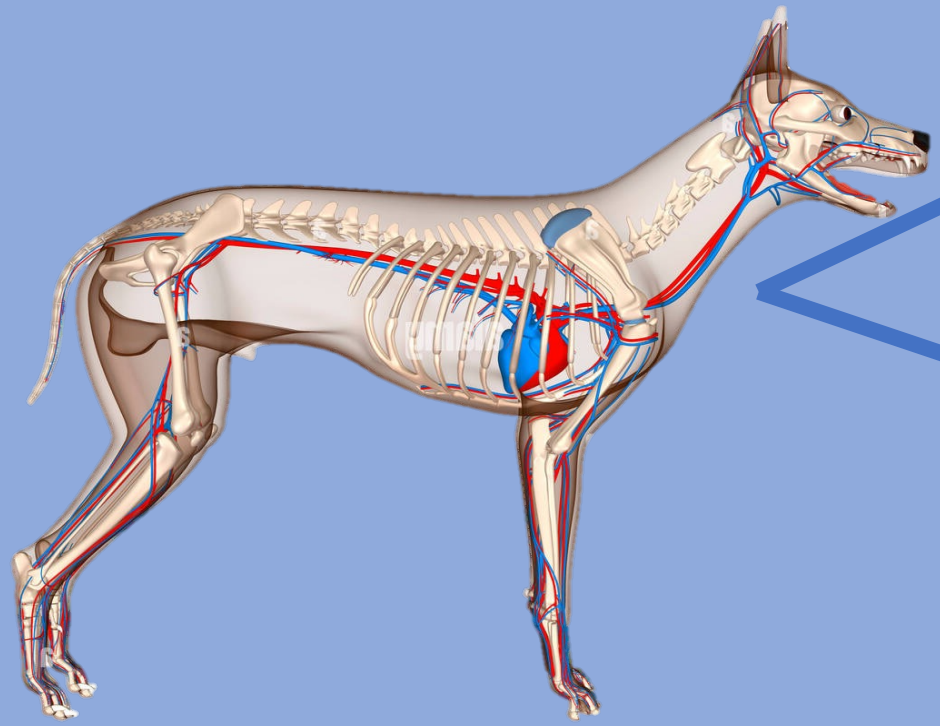


Mycosis Fungoides **Pagetoid Reticulosis**

- Generalized exfoliative erythroderma
- Mucocutaneous depigmentation
- Erosions / ulcers
- Cutaneous nodules or plaques
- Infiltrative mucosal lesions
- Vesiculobullous variants

Cutaneous Epitheliotropic Lymphoma

Clinical Signs



Mycosis Fungoides **Pagetoid Reticulosis**

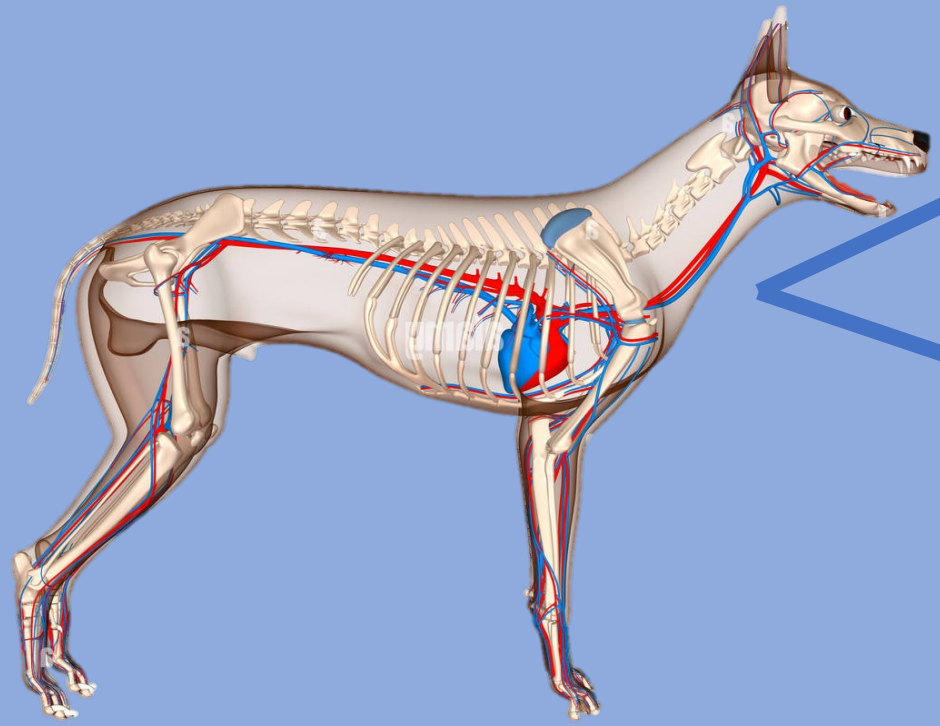
Difference is histopathologic:

PR: infiltrate in epidermis and adnexa

MF: infiltrate also in dermis

Cutaneous Epitheliotropic Lymphoma

Clinical Signs



1. Exfoliative Erythroderma

2. Mucocutaneous Form

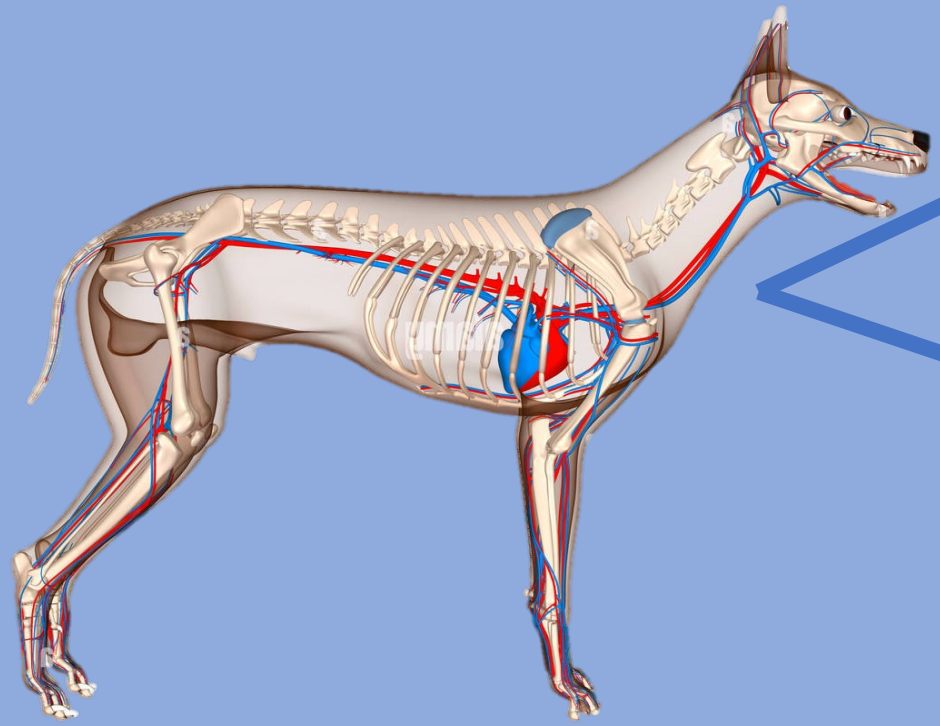
3. Solitary/Multifocal Nodules

4. Oral Ulcerative Disease

Figure 1. Showing representative images of the 4 categories of clinical presentation in dogs

Cutaneous Epitheliotropic Lymphoma

Clinical Signs

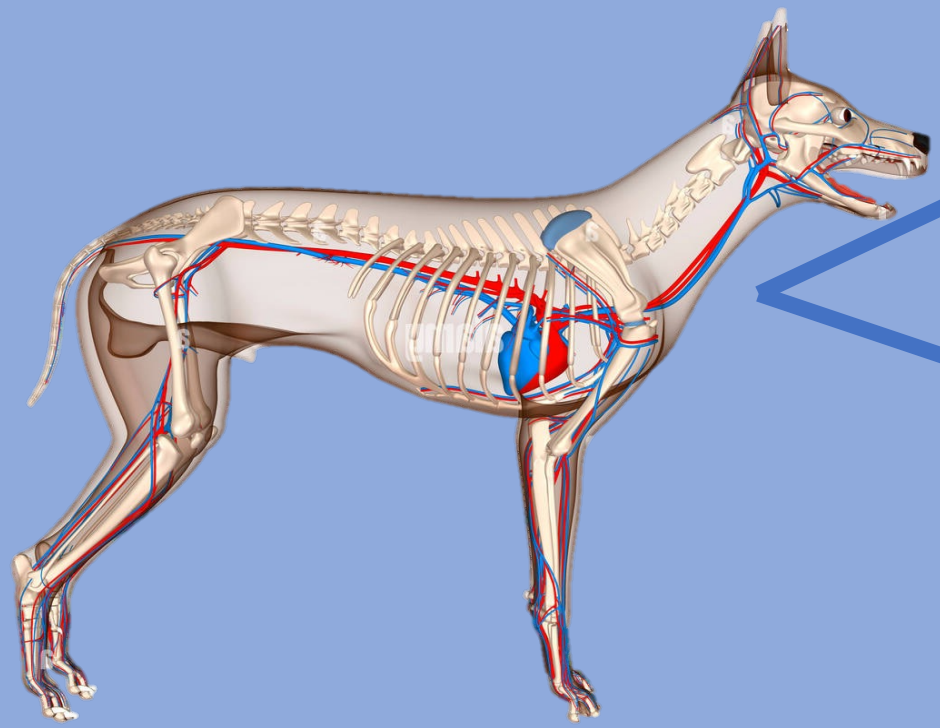


Sezary Syndrome

- **Progressive form of MF**
- **Skin lesions + leukemia**
  - **Sezary cells – neoplastic lymphocytes in peripheral blood**
- **Extremely rare**

Cutaneous Epitheliotropic Lymphoma

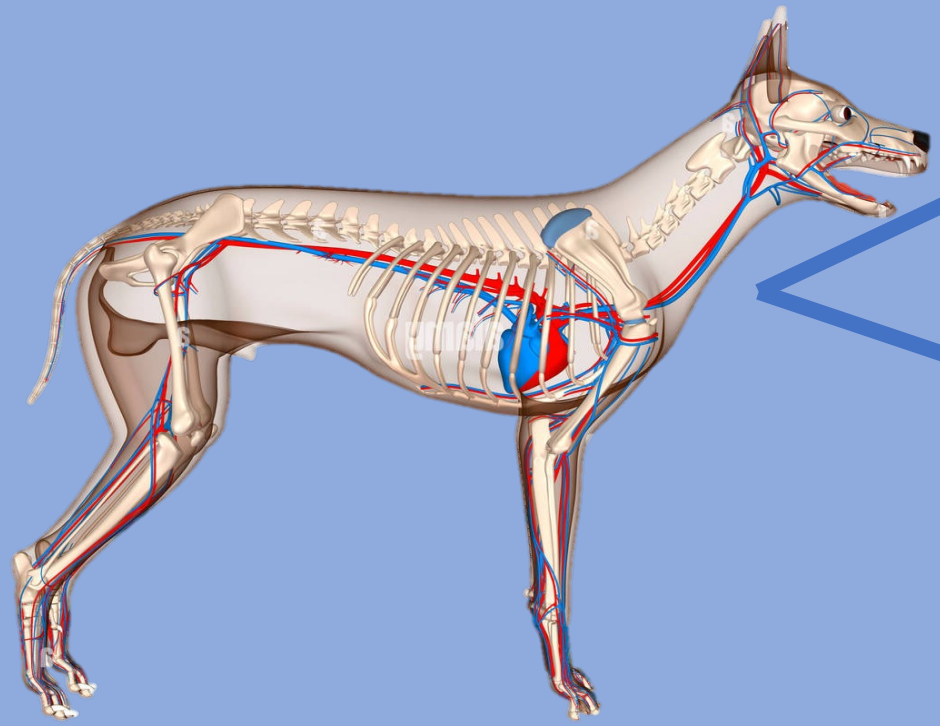
Treatment/Prognosis



- <u>Treatment:</u> No standard of care
  - Chemotherapy
  - Non-chemotherapeutics
    - Retinoids
    - Safflower oil
    - Apoquel
    - Cytopoint?
    - Glucocorticoids
  - Radiation

Cutaneous Epitheliotropic Lymphoma

Treatment/Prognosis



- **<u>Prognosis:</u> Poor. Euthanasia usually due to poor quality of life**
  - **Disseminated disease rare**
  - **MST 6 months**
  - **MST longer if mucosal vs. skin lesions (491 vs. 130 days)**

Cutaneous Epitheliotropic Lymphoma

Etiology/Signalment

- **Pathogenesis:** Less is known. Likely CD_{8+} T-cells
- **Signalment:** Median 13.5 yo. No sex or breed predilection

Cutaneous Epitheliotropic Lymphoma

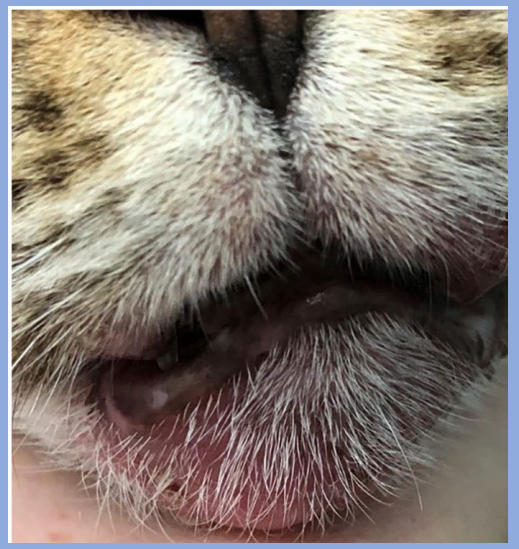
Clinical Signs

- **Varied**
- **Single or multifocal**
- **Exfoliative erythroderma**
- **Patch, plaque**
- **+/- pruritus**

Distribution:

- **Face, eyelids, mucocutaneous junctions, elbows, trunk > oral cavity**

Cutaneous Lymphoma



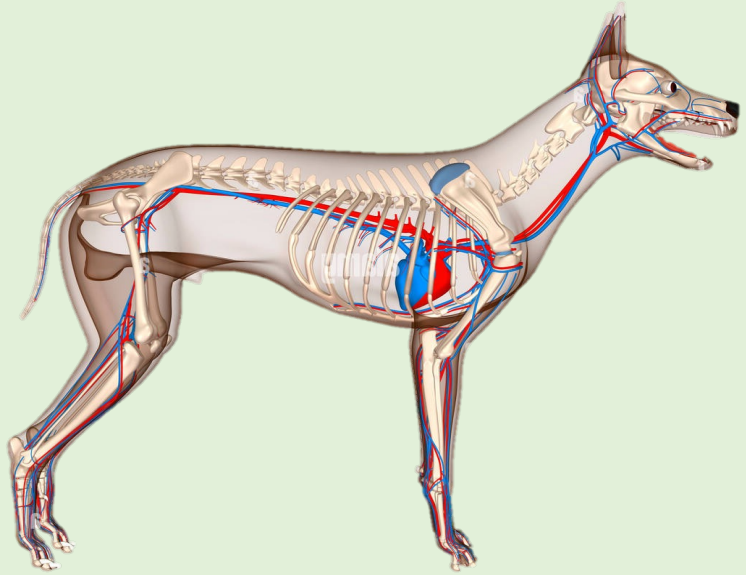
Cutaneous Epitheliotropic Lymphoma

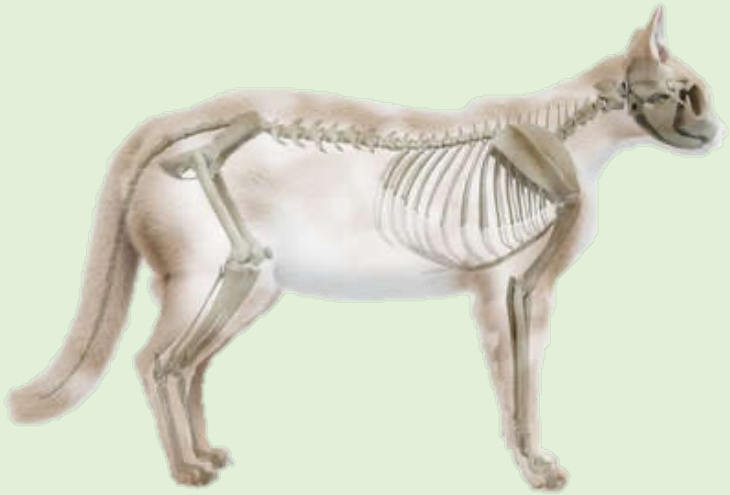
Treatment/Prognosis

- **Treatment:** No studies evaluating efficacy of any chemotherapeutic agent on survival time. Reported use of:
  - Radiation
  - Chemotherapeutics (vincristine, lomustine, cyclophosphamide)
  - Fibronectin

- **Prognosis**: MST 10-25 months, range 4 years

Cutaneous Non-Epitheliotropic Lymphoma



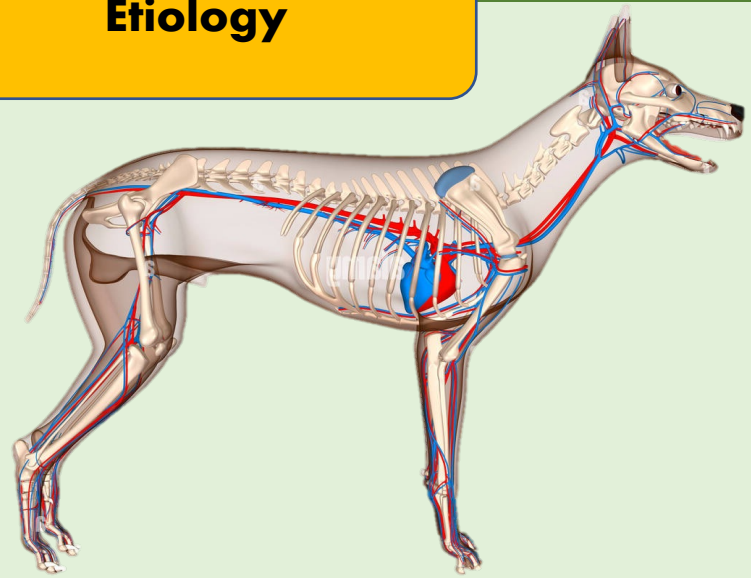


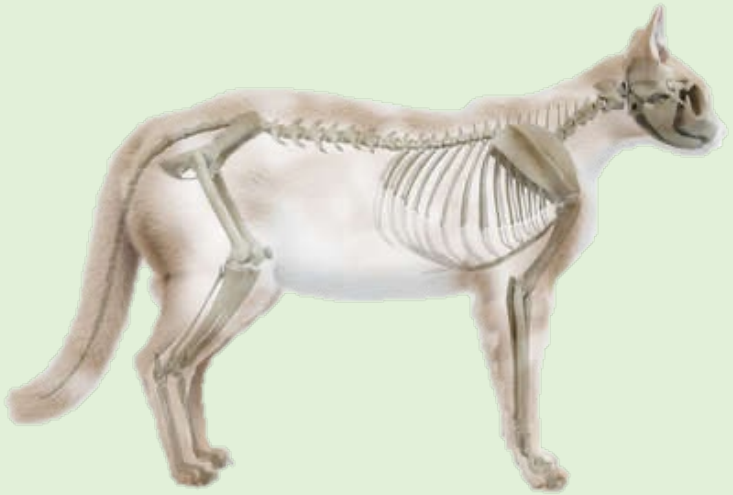
Neoplastic lymphocytes in dermis and SQ

Likely represents diverse as yet poorly characterized conditions

Cutaneous Non-Epitheliotropic Lymphoma

Etiology



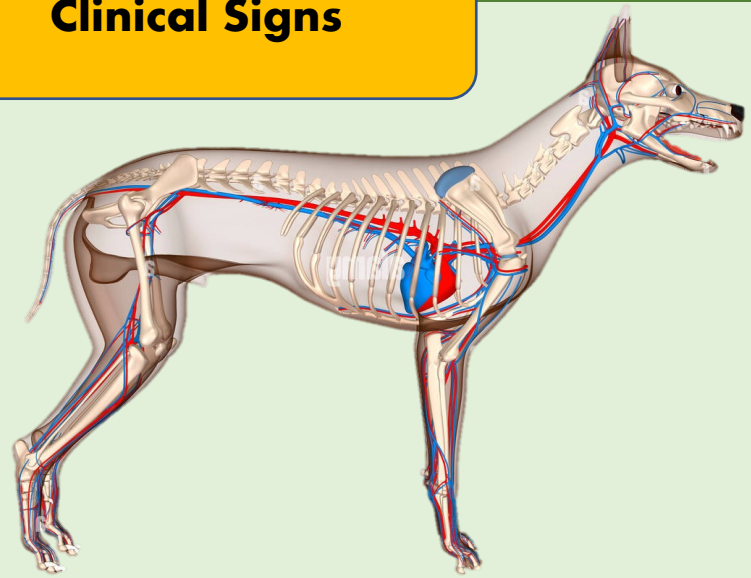


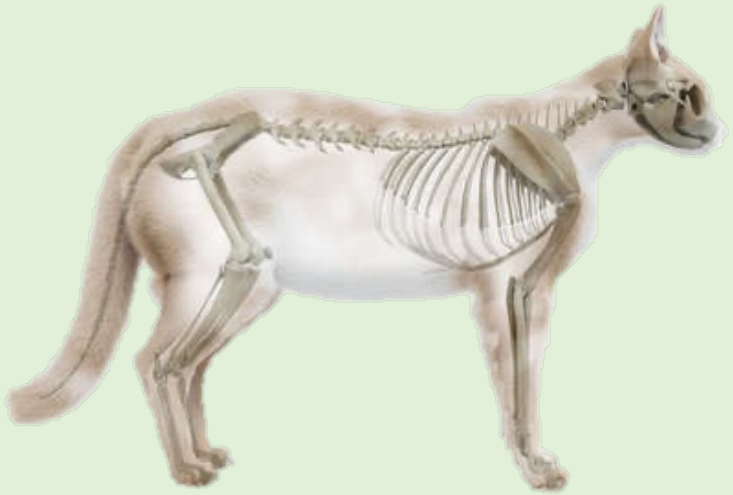
Pathogenesis:

- **Infiltrating lymphocytes are usually T-cells**
  - **Mostly CD_8+**
  - **Remainder are CD_4- CD_8- T-cells**
- **Different categories of T-cell non-epitheliotropic cutaneous lymphomas**
  - **Unknown clinical significance**
  - **Most are called *peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS)***

Cutaneous Non-Epitheliotropic Lymphoma

Clinical Signs

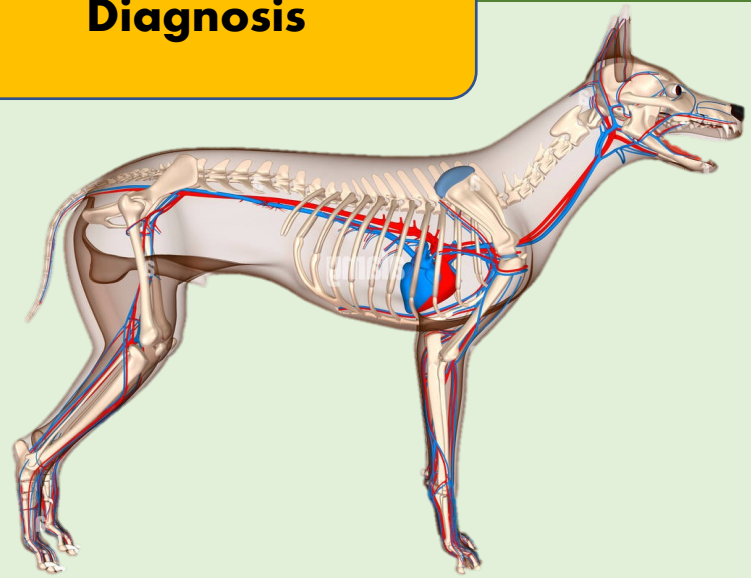


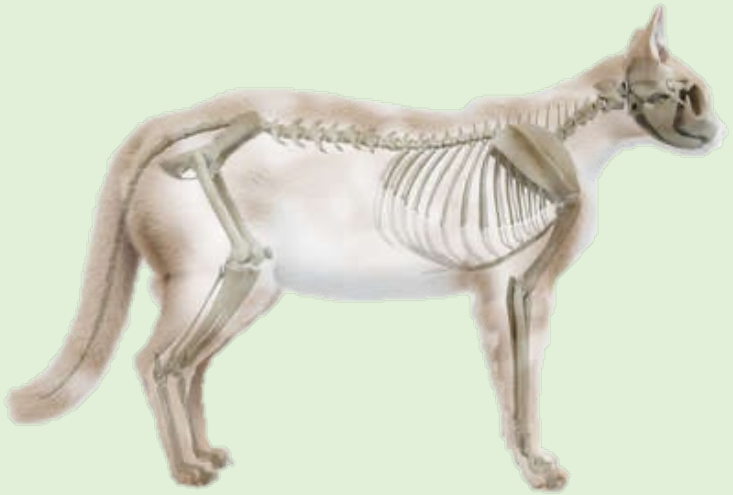


- **Variable presentations**
- **Single, multiple, or diffuse SQ nodules, slow or rapid growth**
  - **DDx panniculitis**
- **Common rapid metastasis to lymph nodes and systemic**
- **+/- Paraneoplastic hypercalcemia**

Cutaneous Non-Epitheliotropic Lymphoma

Diagnosis

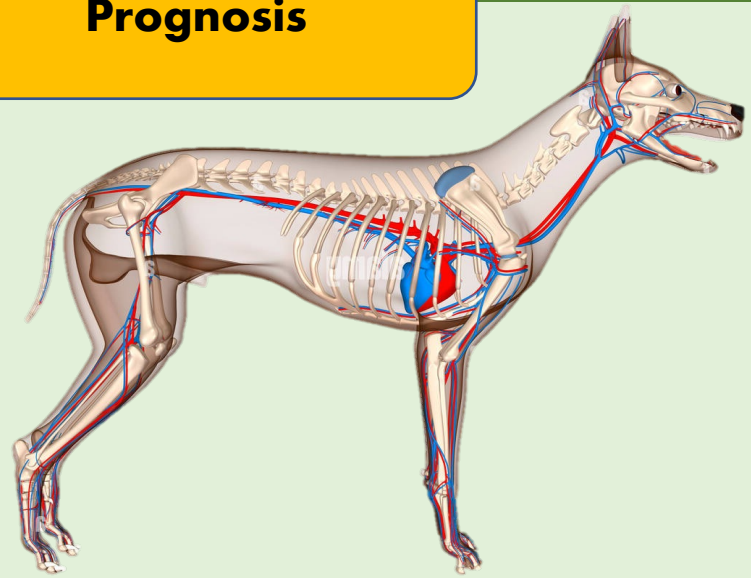


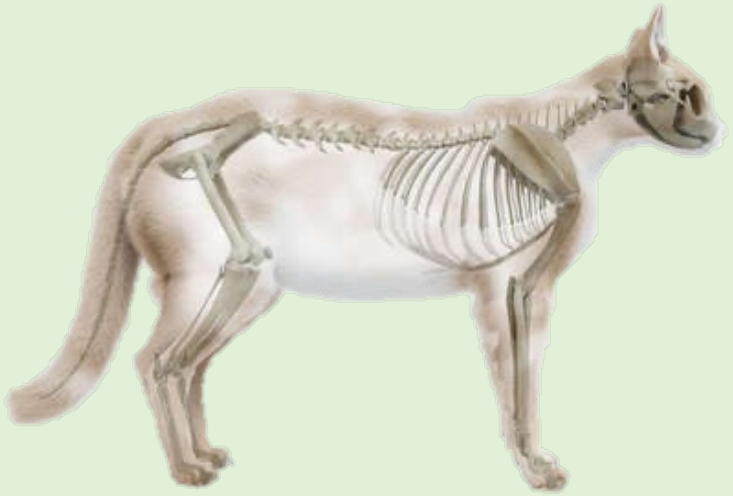


- **Challenging**
- **Canine inflamed non-epitheliotropic cutaneous lymphomas**
  - **Similar histopathologically to histiocytic diseases**
  - **PARR testing and IHC less diagnostic - marked (polyclonal) reactive lymphoid infiltrate.**
- **Immunophenotyping – prognostic**

Cutaneous Non-Epitheliotropic Lymphoma

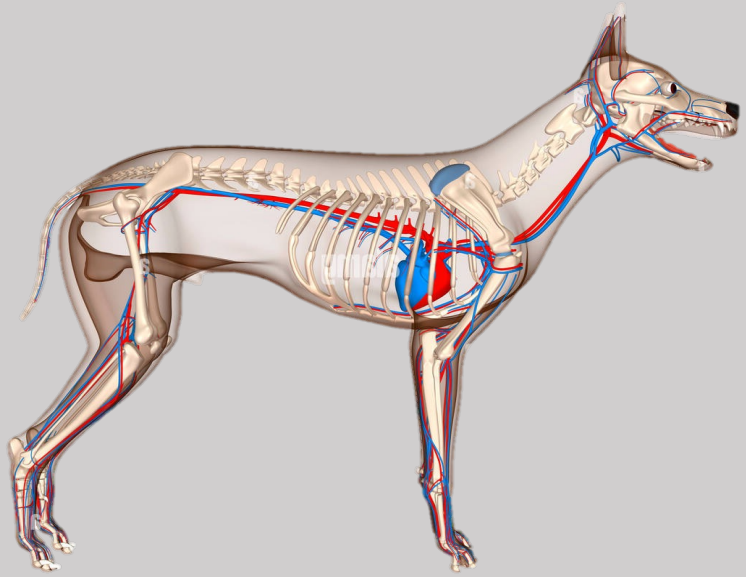
Prognosis





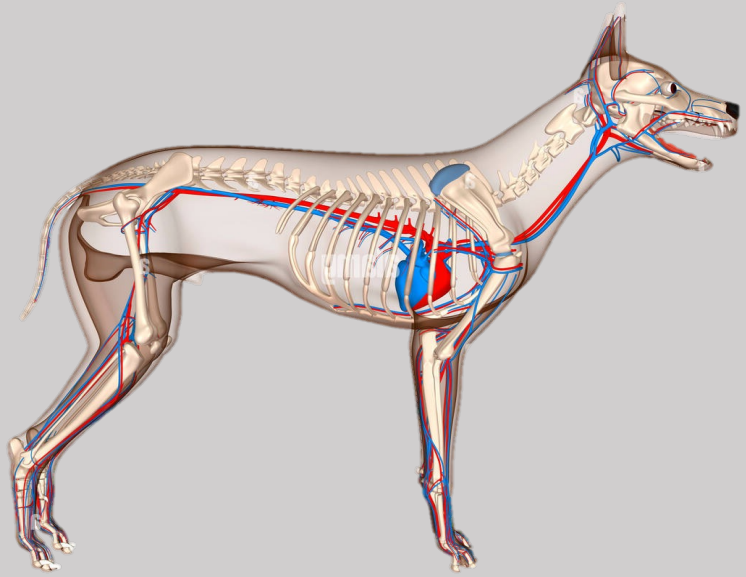
- **Canine B-cell lymphomas have longer MST than T-cell, with the opposite true for cats.**
- **Poor overall - short-lived remissions, no cure**

Cutaneous Lymphocytosis



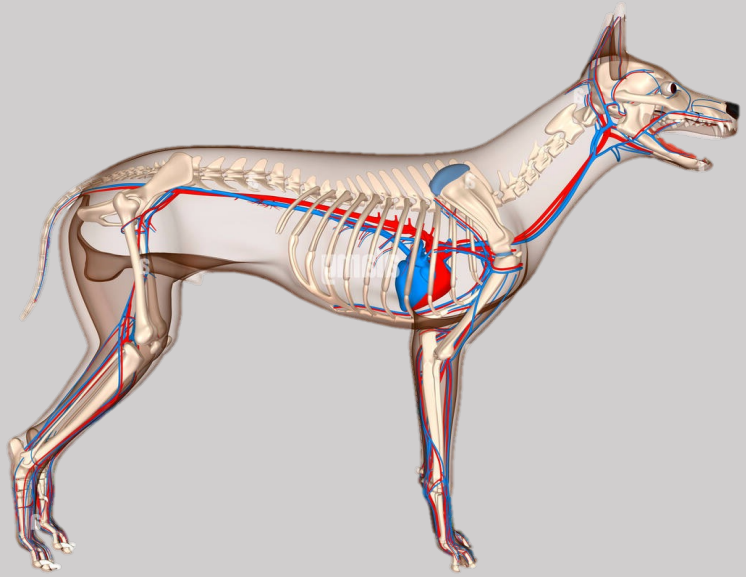
- Variably named – confusing
  - Synonyms; cutaneous pseudolymphoma, lymphocytoma cutis, cutaneous lymphoid hyperplasia, indolent lymphoma
- Very rare (cats > dogs)

Cutaneous Lymphocytosis



- **Etiology: unknown**
- **Indolent, slowly progressive cutaneous lymphoma?**
  - **Monoclonal lymphoid populations**
  - **May transform to high grade lymphoma**

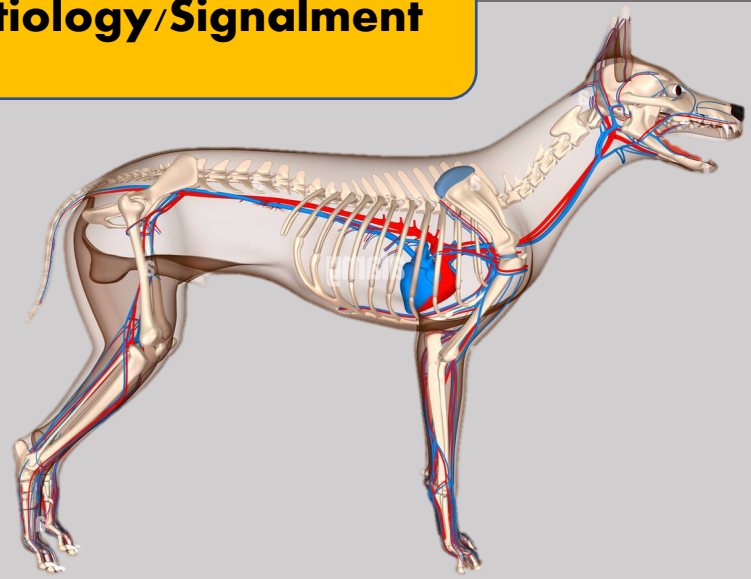
Cutaneous Lymphocytosis



- **Diagnosis:**
  - **Histopathology**
  - **IHC**
  - **PARR (*caution interpreting*)**
- **Prognosis: Guarded but unpredictable**
  - **Systemic progression possible after years of stability**
  - **Spontaneous regression possible (N=1 dog)**

Cutaneous Lymphocytosis

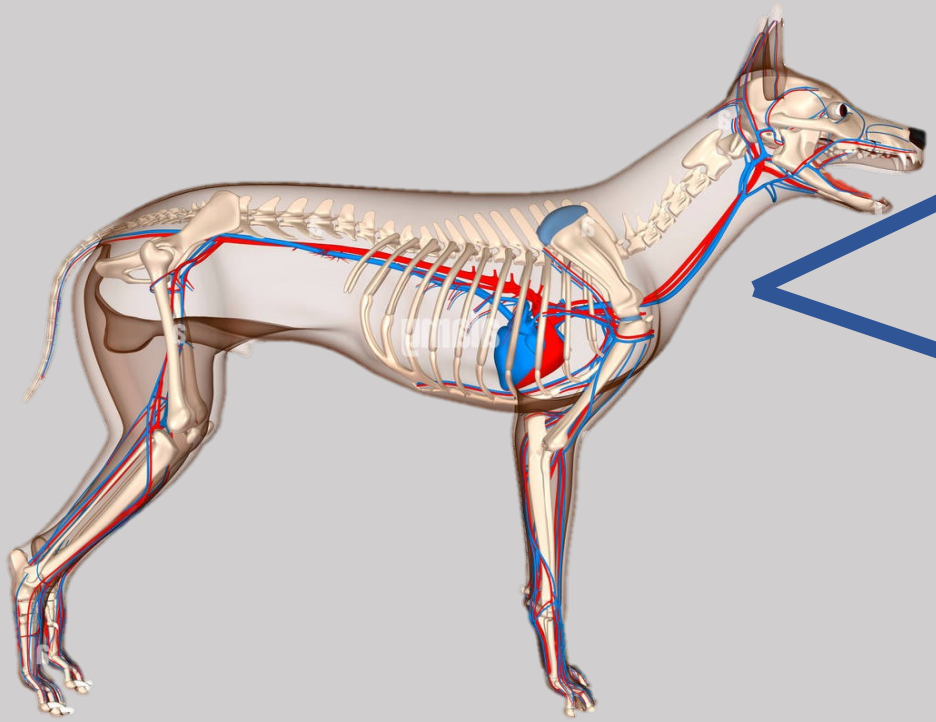
Etiology/Signalment

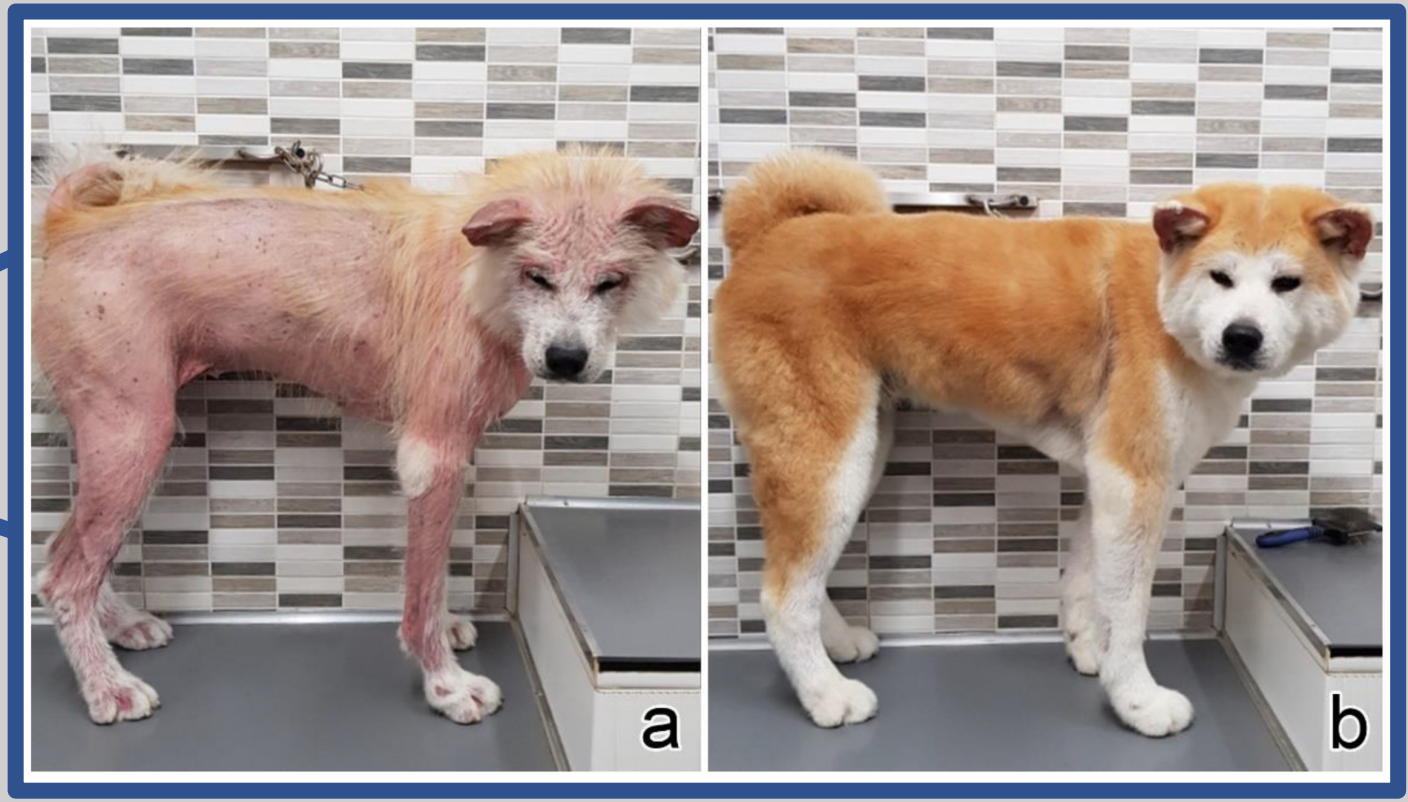


- **Pathogenesis:** Most infiltrating lymphocytes are CD_{3+} T-cells. May co-express CD_{8+}.
  - May have aggregates of CD_{20+} B-cells in infiltrate
  - Most are alpha-beta T-cells (dogs)
- **Signalment:** Older age

Cutaneous Lymphocytosis

Clinical Signs

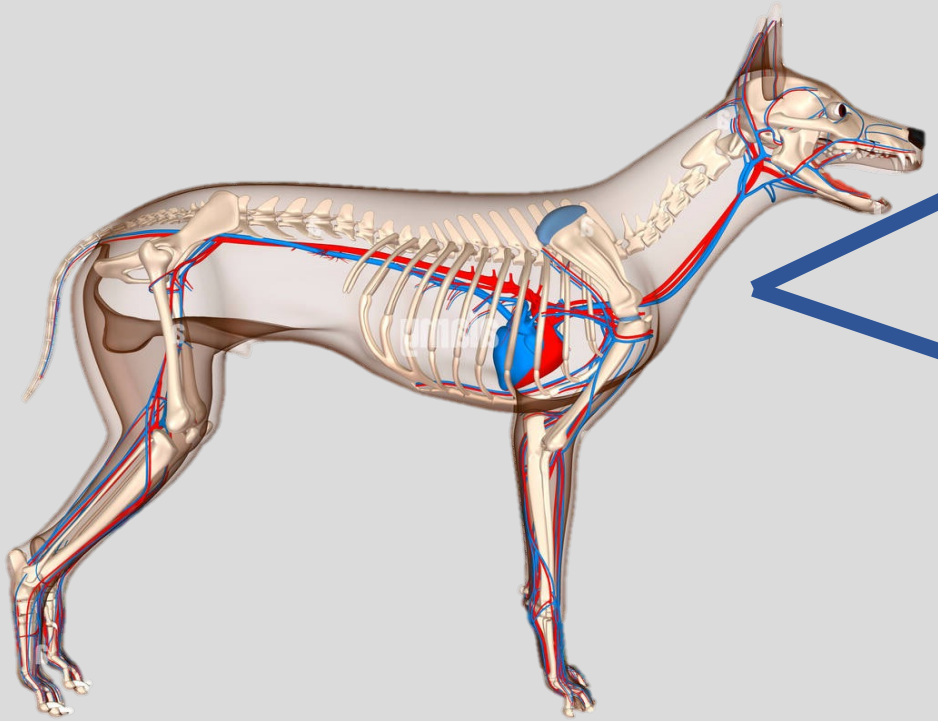




https://doi.org/10.3390/vetsci9010026

Cutaneous Lymphocytosis

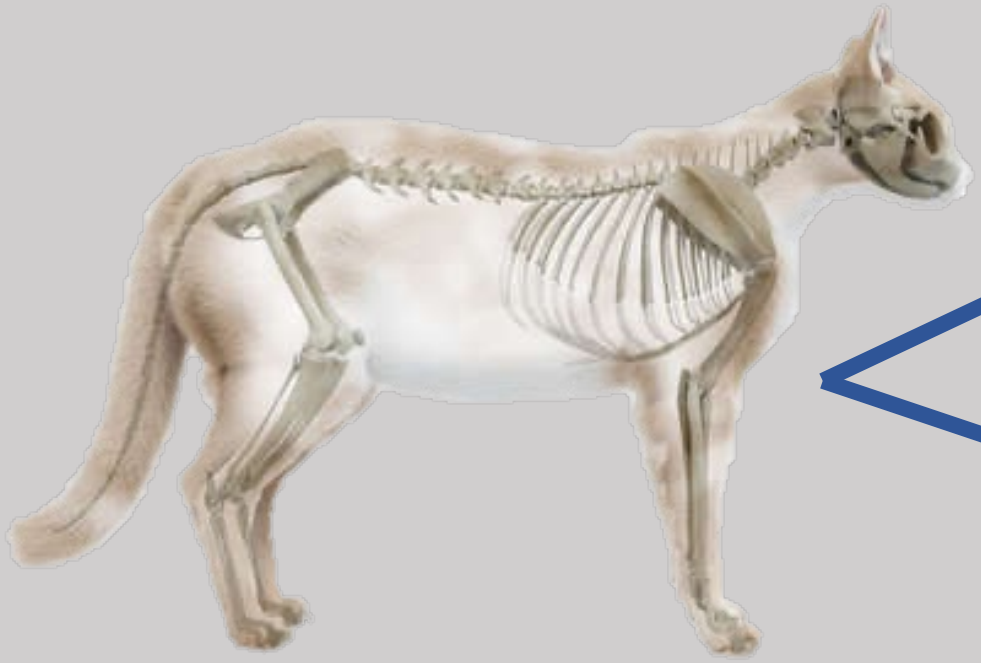
Clinical Signs

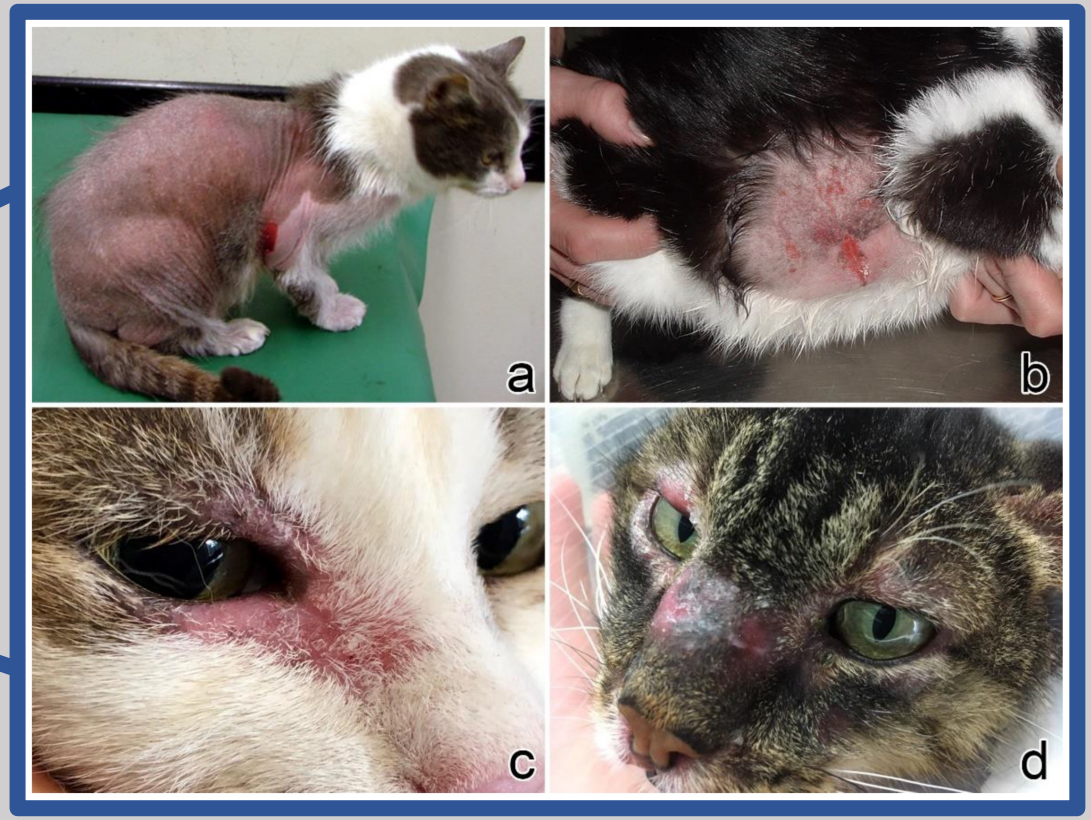


https://doi.org/10.3390/vetsci9010026

Cutaneous Lymphocytosis

Clinical Signs

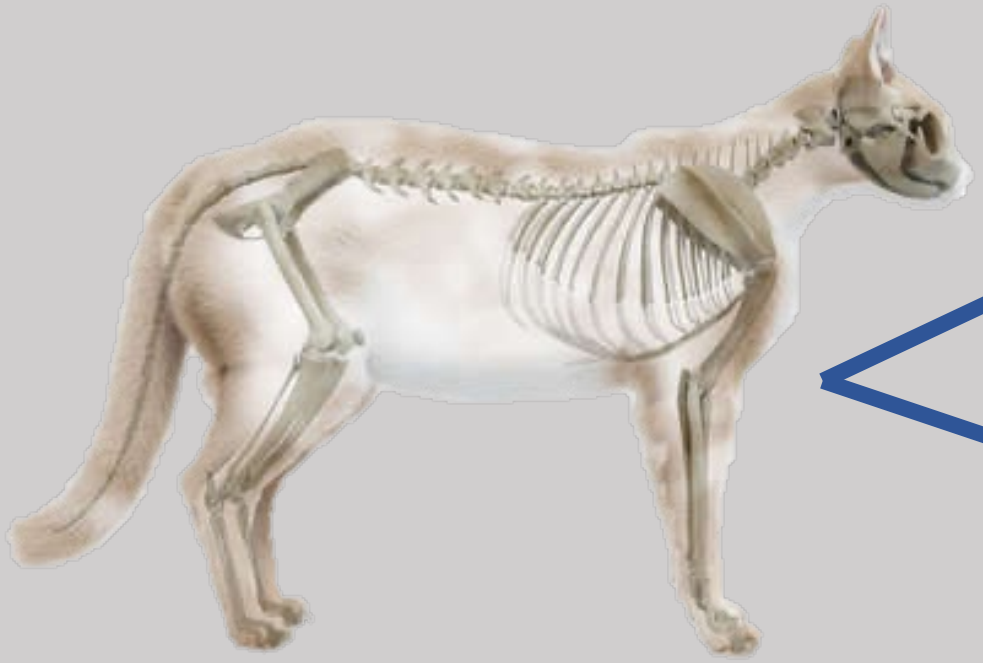




https://doi.org/10.3390/vetsci9010026

Cutaneous Lymphocytosis

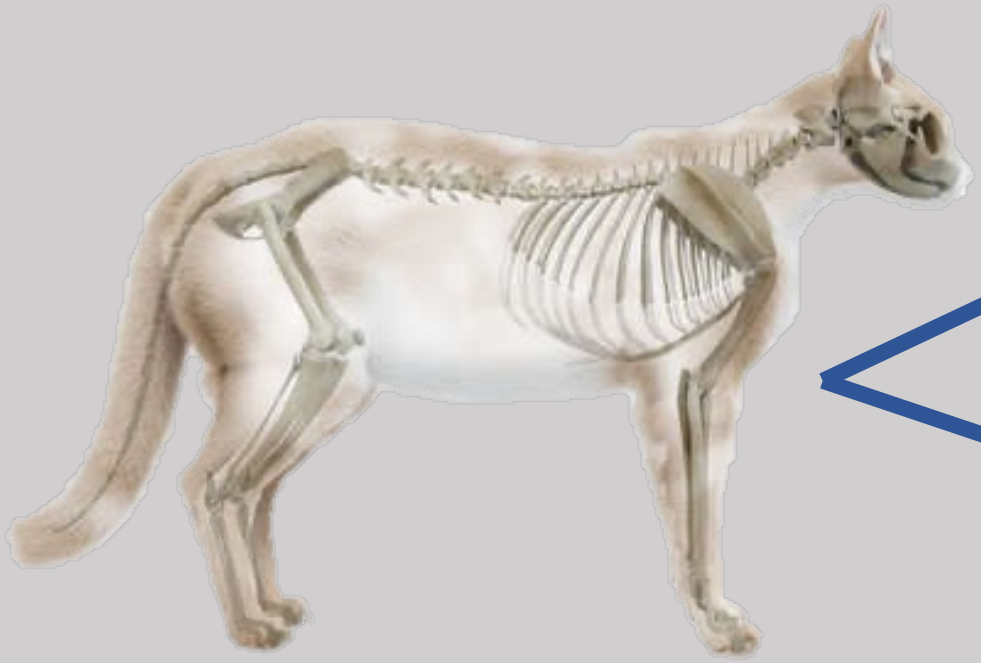
Clinical Signs



Courtesy of Dr. Lydia Harbour

Cutaneous Lymphocytosis

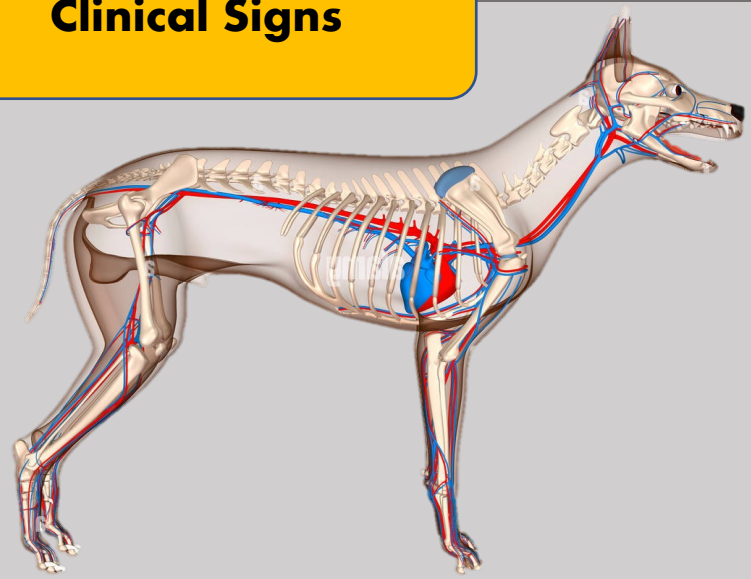
Clinical Signs



Courtesy of Dr. Amy Schumaker

Cutaneous Lymphocytosis

Clinical Signs

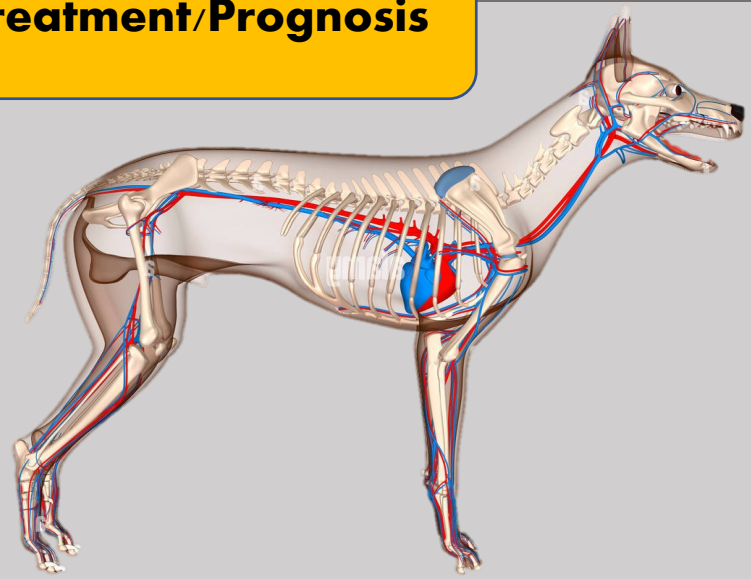


SYSTEMIC SIGNS

- +/- **Peripheral lymphadenopathy**
- +/- **Other systemic signs (rare)**

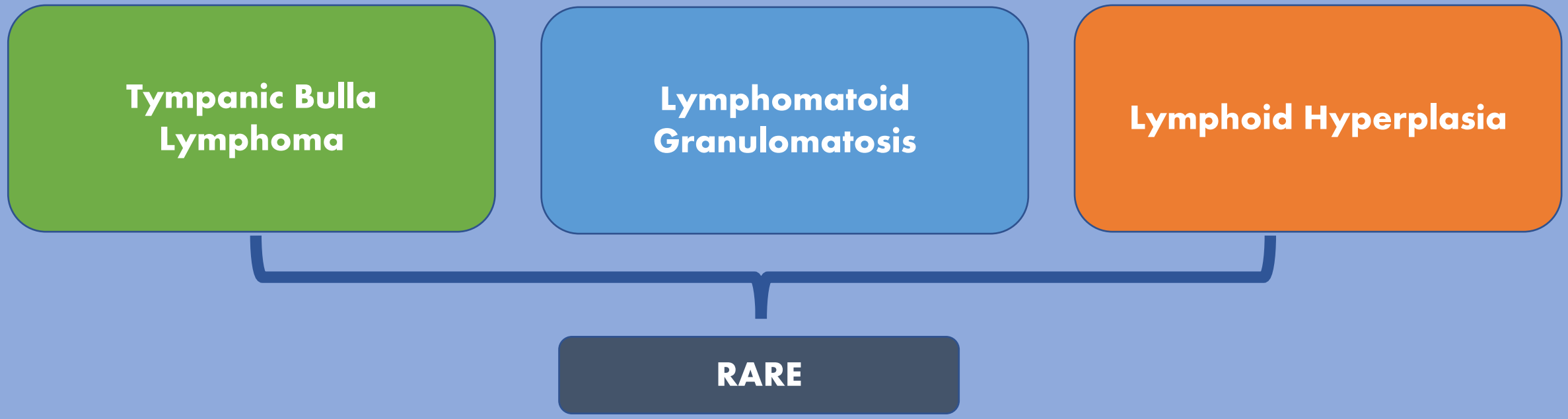
Cutaneous Lymphocytosis

Treatment/Prognosis

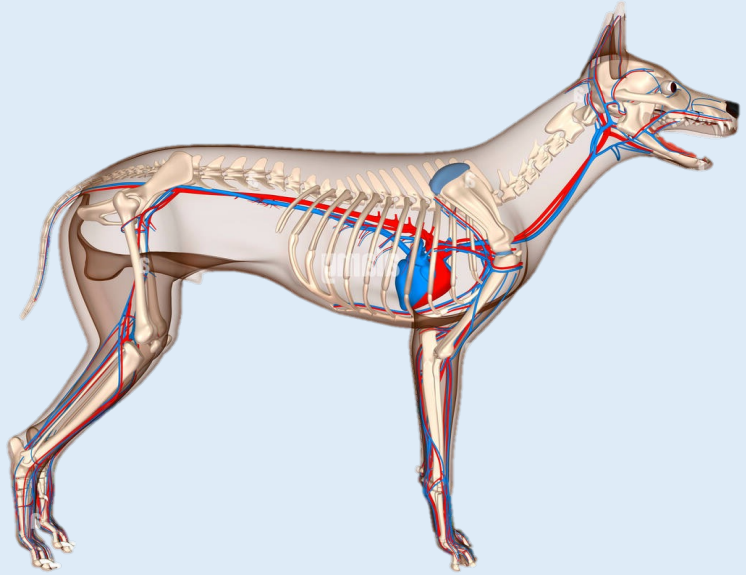


- **<u>Treatment:</u> No established protocol. Steroids most commonly used.**

Cutaneous Lymphoproliferative Disorders



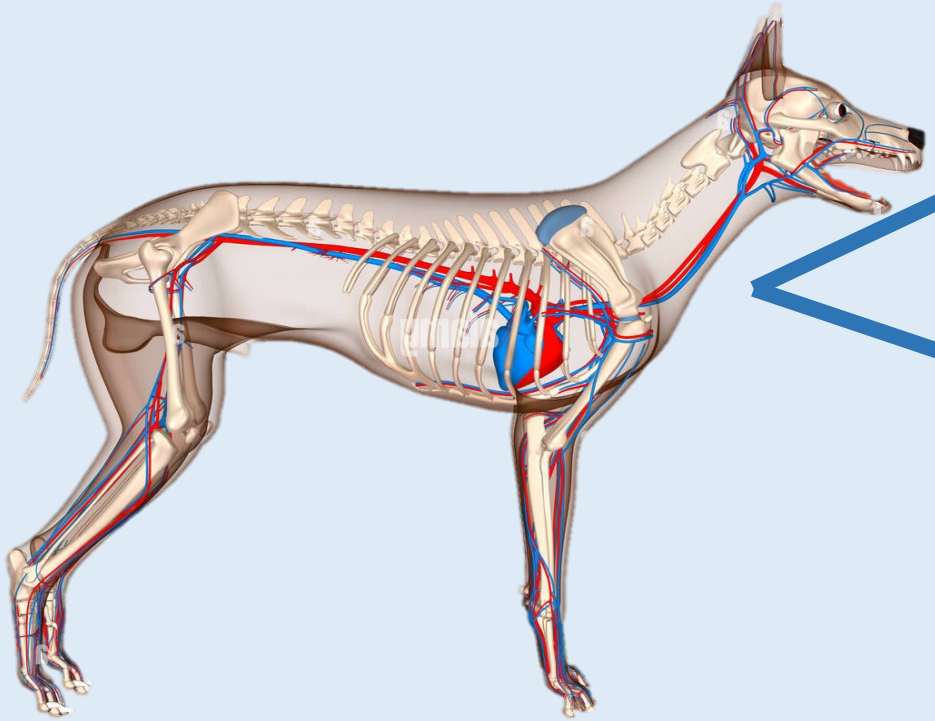
Lymphomatoid Granulomatosis



- Rare lymphohistiocytic proliferative disorder
- Infiltrating lymphocytes primarily CD_3, CD_{20}, and CD_{79} positive
- Atypical non-epitheliotropic T-cell lymphoma?
- Systemic signs consistently

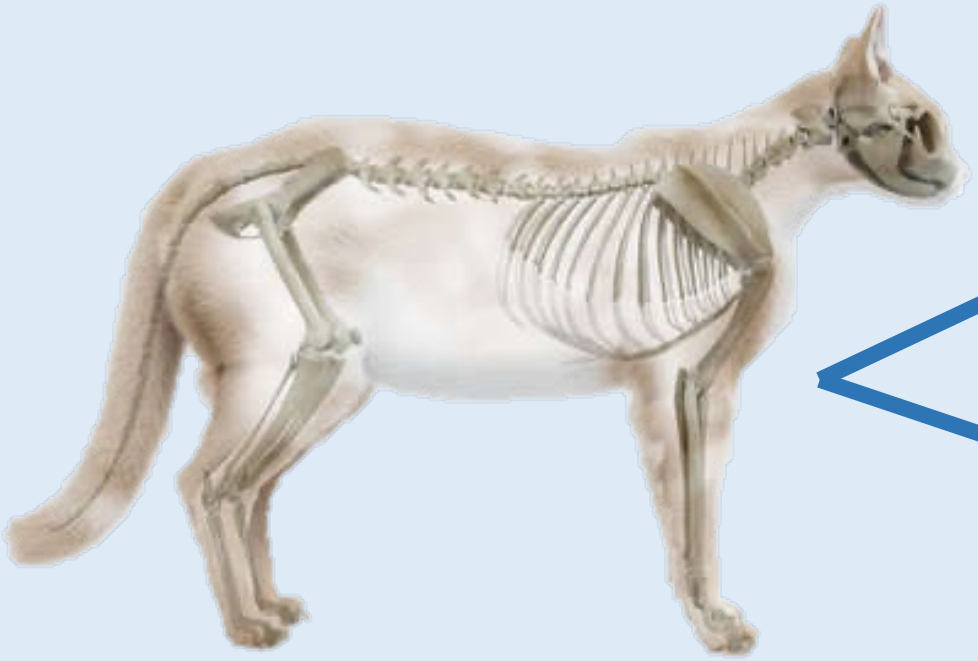
Clinical Signs

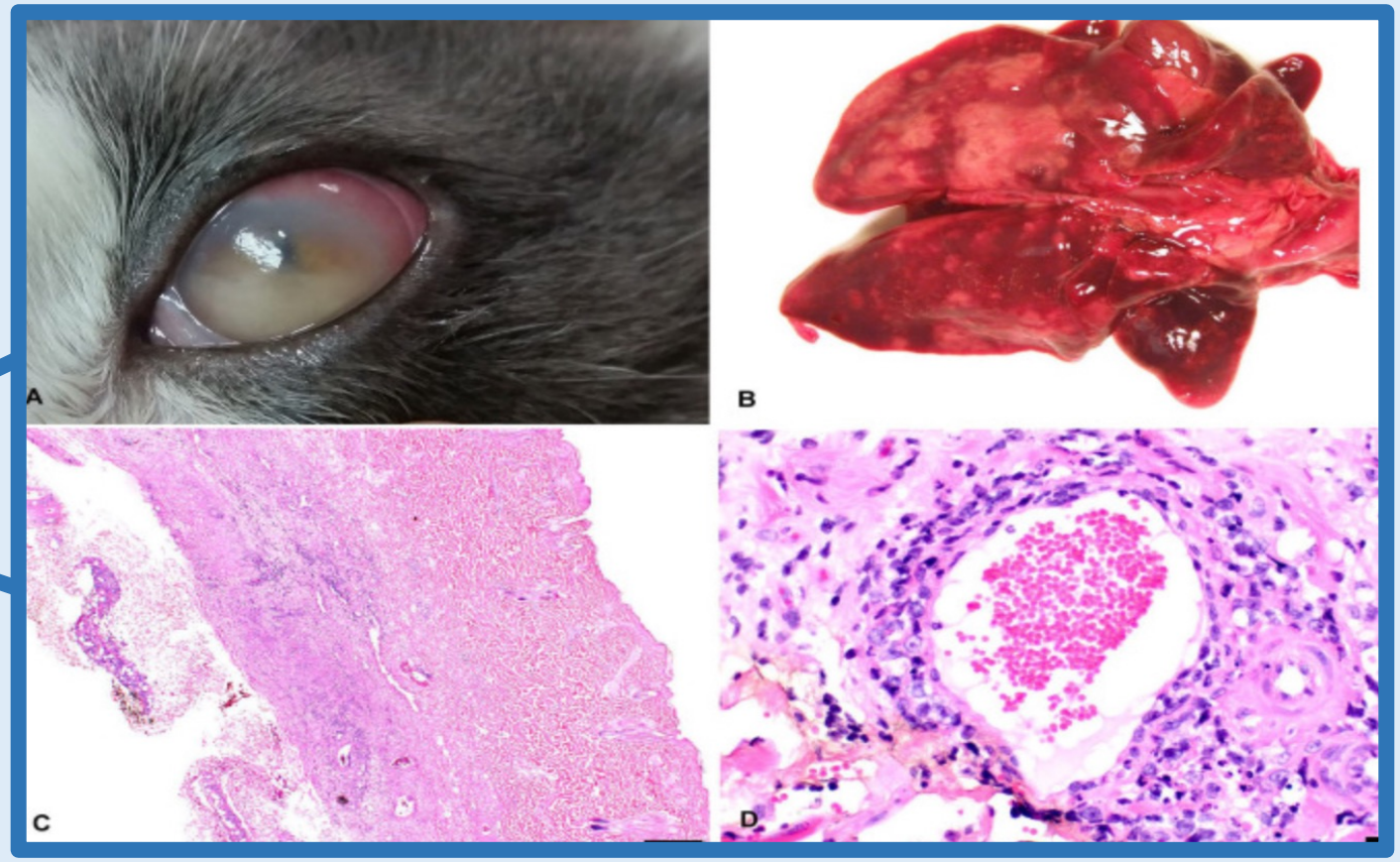
Lymphomatoid Granulomatosis



Clinical Signs

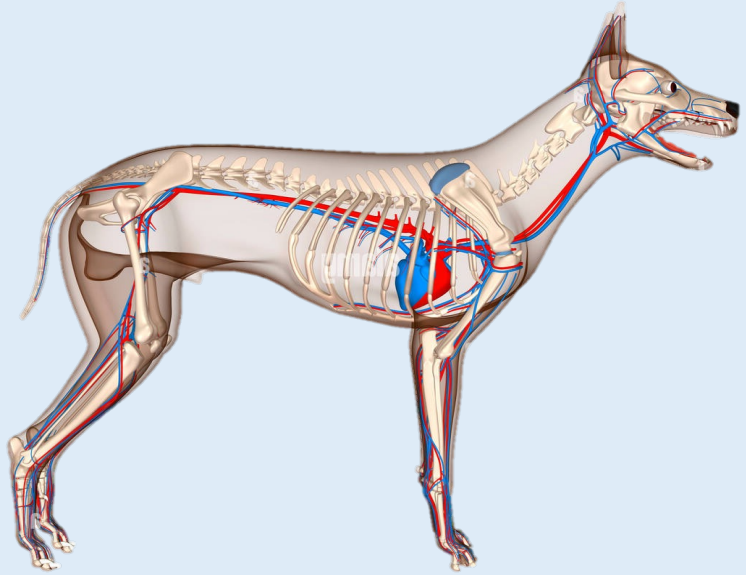
Lymphomatoid Granulomatosis





Clinical Signs

Lymphomatoid Granulomatosis

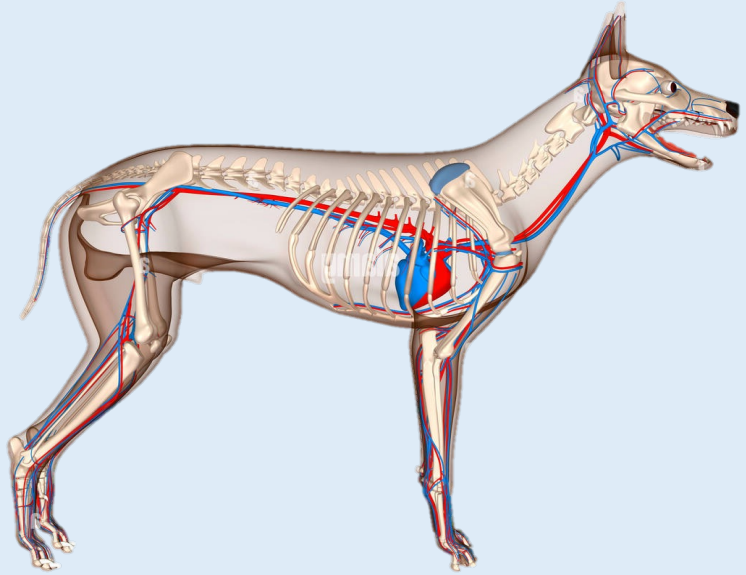


SYSTEMIC SIGNS:

- Systemic involvement primarily LUNG
- Also lymph nodes, liver myocardium mesenteric fat, kidney, pancreas, adrenal gland, colon, skeletal muscle, bone marrow oral cavity, periocular thyroid, synovium
- Eosinophilia, lymphocytosis, hyperglobulinemia

Treatment/ Prognosis

Lymphomatoid Granulomatosis



- **Treatment:** Chemotherapy
- **Prognosis:** Poor
  - Dog - MST 3 months (range 0 to 4 years)
  - Cat – MST < 2 months
  - Euthanasia frequently due to respiratory distress
  - Remission with chemotherapy rare but possible (dog)

Tympanic Bulla Lymphoma

- Otitis media / interna (cats)
- T-cell > non-B non-T cell origin
- Poor prognosis

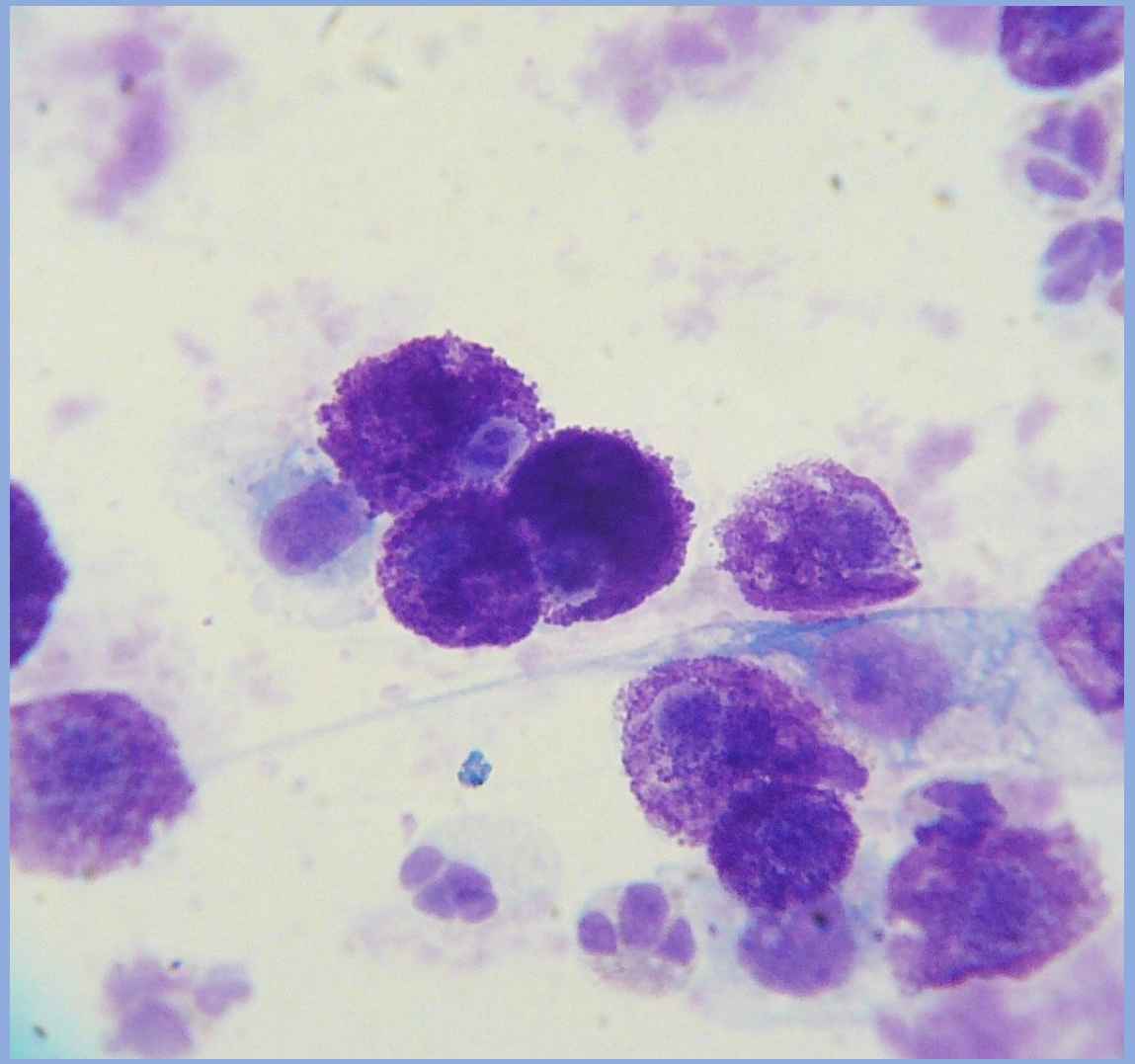
Lymphoid Hyperplasia

Histopathology	May look like neoplasia!
Clonality	Polyclonal Mainly T-cell
Disease progression	Benign
Lymph node biopsy	

N=1 cat

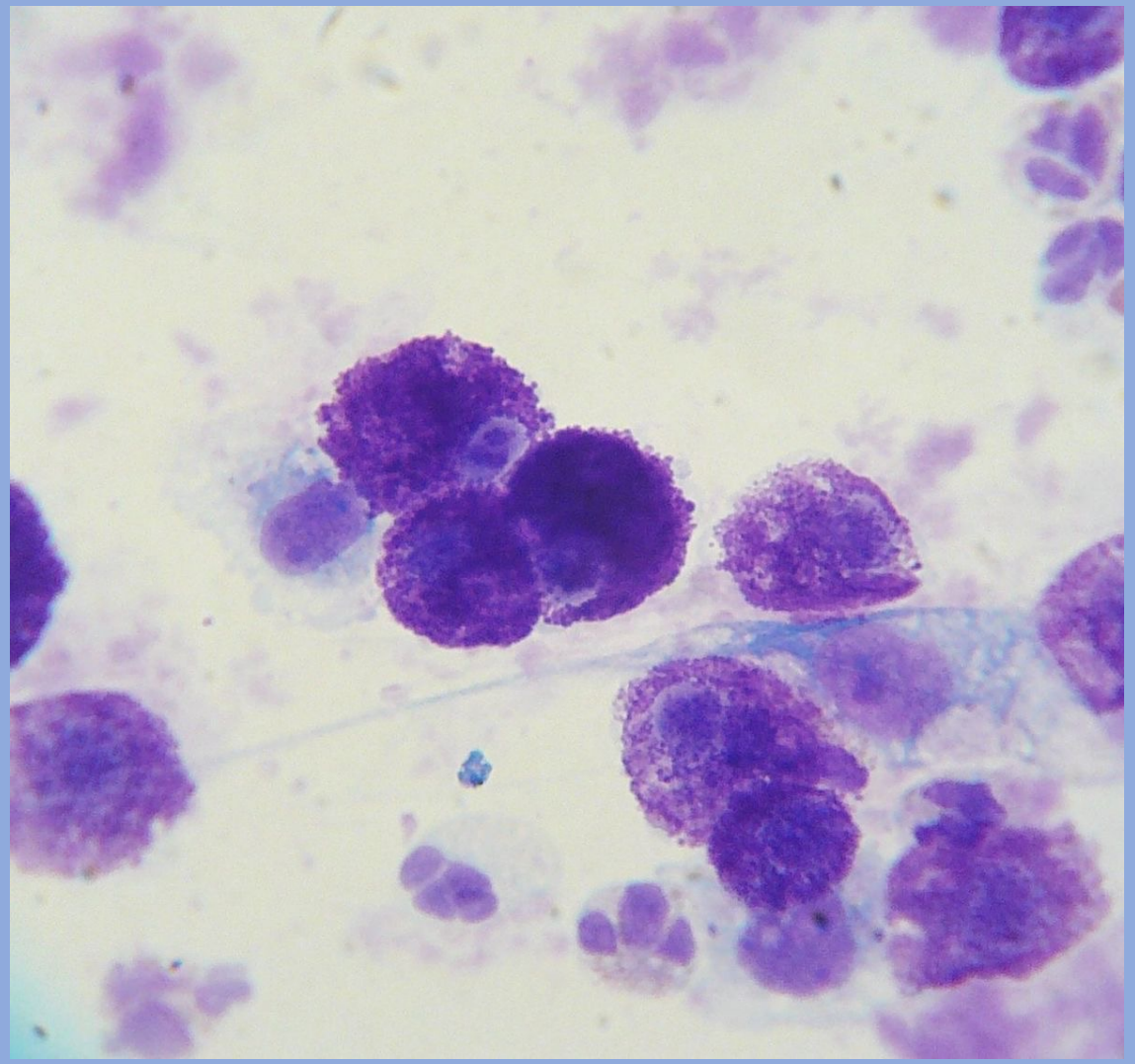
Case 2

Cytology



Diagnosis?

Cytology



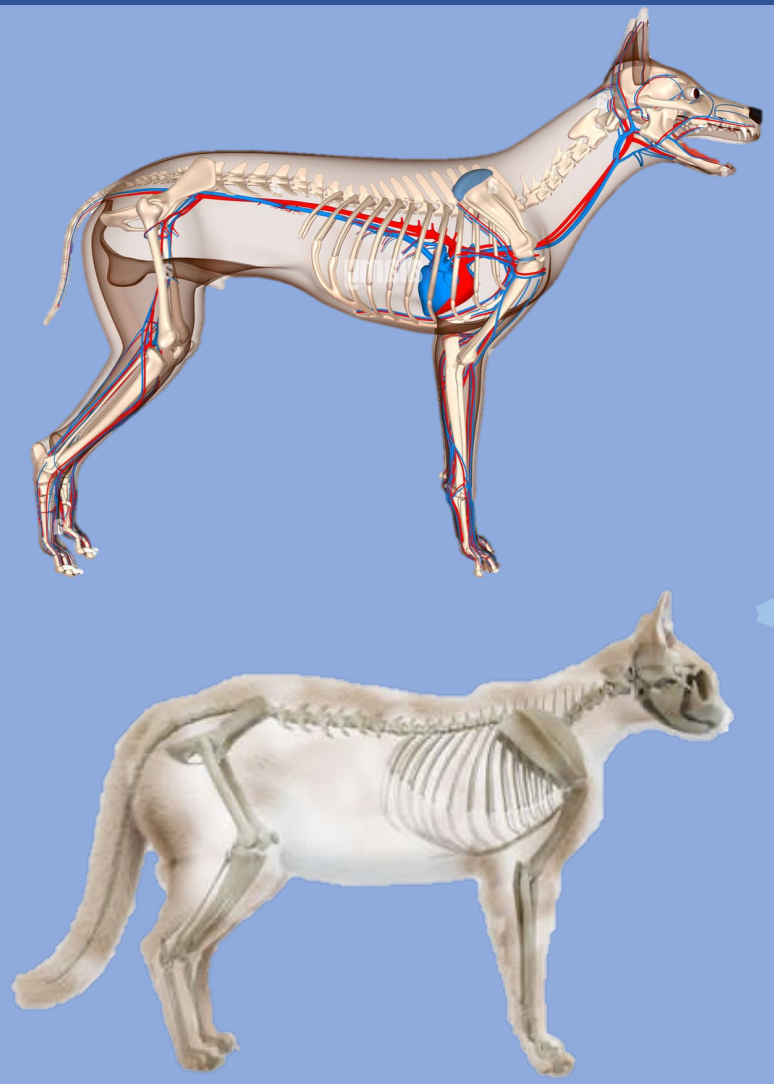
Mast cells

Cutaneous Mast Cell Proliferations

4 Types in Dogs and Cats

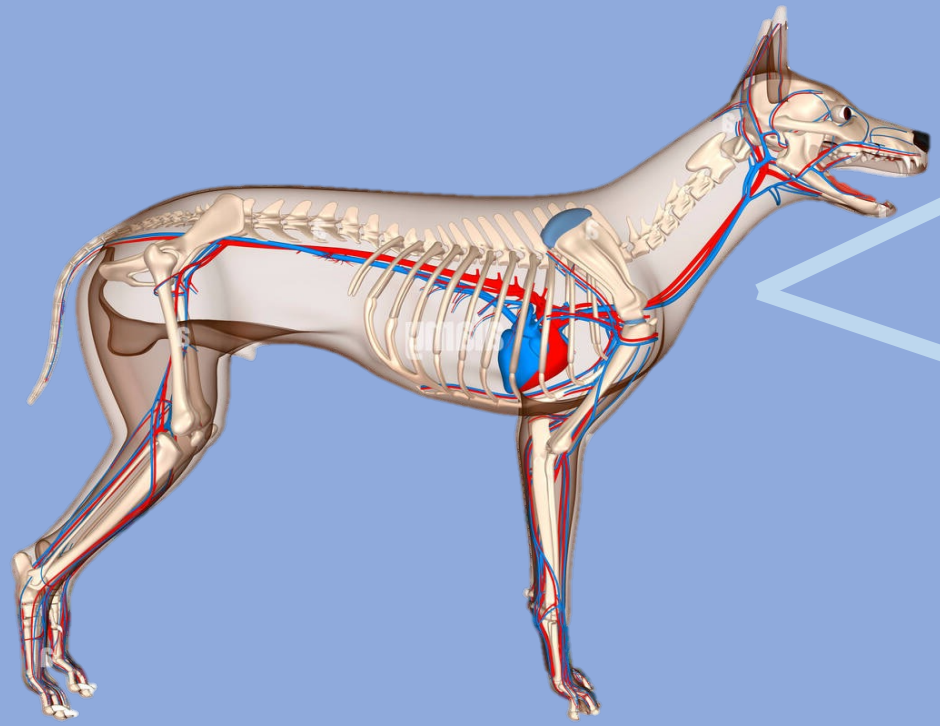
- Mast Cell Tumors
- Urticaria Pigmentosa
- Diffuse Cutaneous Mastocytosis
- Systemic Mastocytosis with Cutaneous Involvement

Mast Cell Tumors



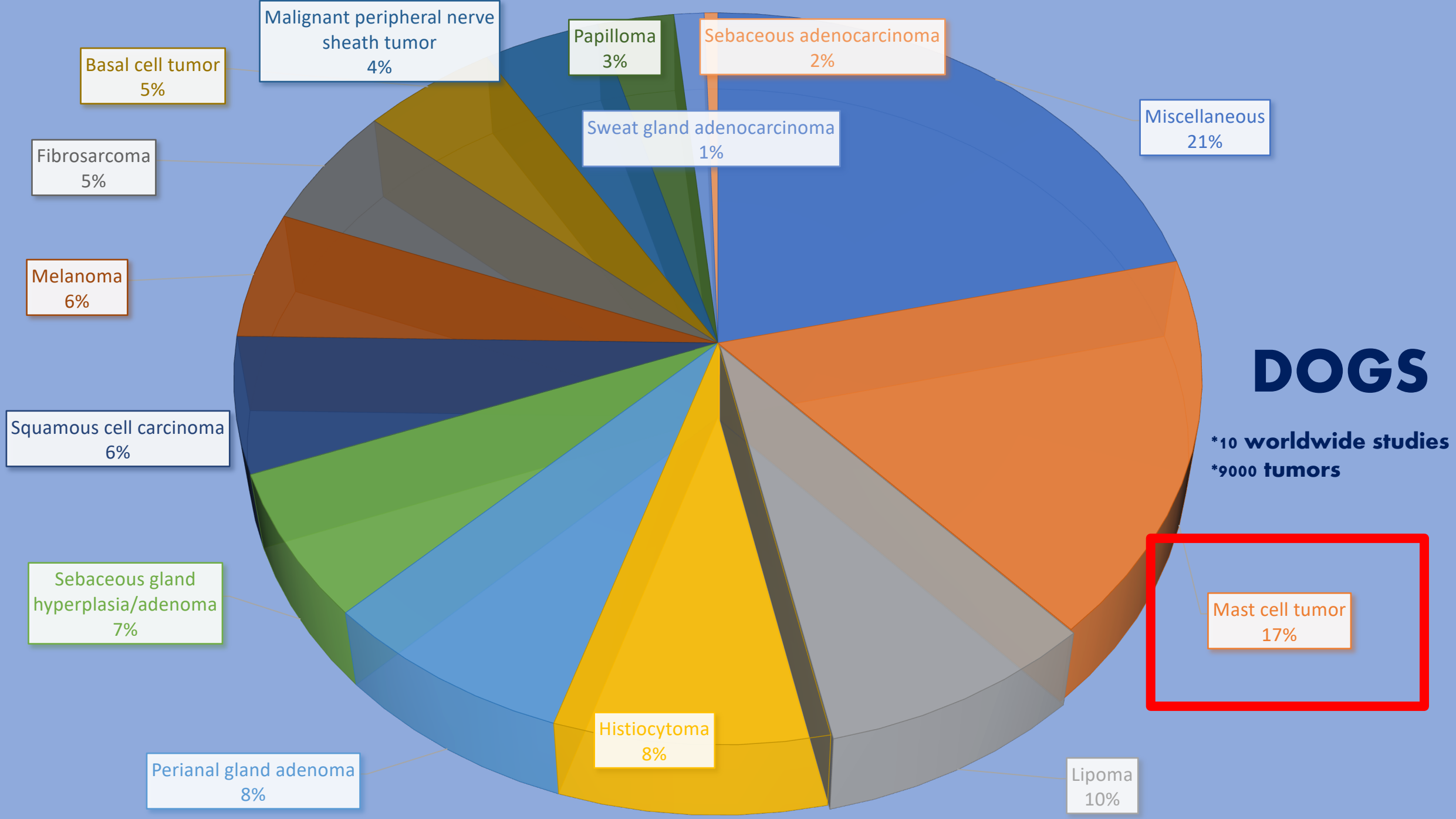
- **Majority: local therapy (surgery +/- radiation)**
- **Minority: metastasis and short survival times**
- **Spontaneous regression: cats, pigs, horses, humans, and one dog**

Mast Cell Tumors



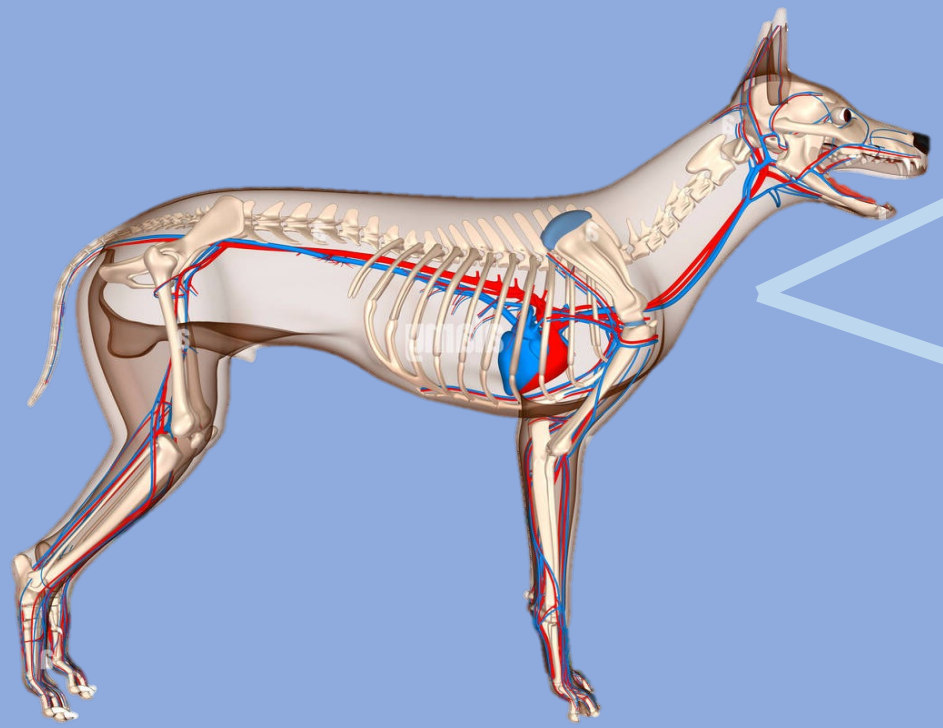
Dog

- **Mast cell sarcoma, mastocytoma**
- **Cutaneous or subcutaneous > visceral**


Malignant peripheral nerve sheath tumor 4%
Papilloma 3%
Sebaceous adenocarcinoma 2%
Basal cell tumor 5%
Sweat gland adenocarcinoma 1%
Miscellaneous 21%
Fibrosarcoma 5%
Melanoma 6%
Squamous cell carcinoma 6%
Sebaceous gland hyperplasia/adenoma 7%
Mast cell tumor 17%
Histiocytoma 8%
Perianal gland adenoma 8%
Lipoma 10%
DOGS
*10 worldwide studies
*9000 tumors

Etiology/Signalment

Mast Cell Tumors

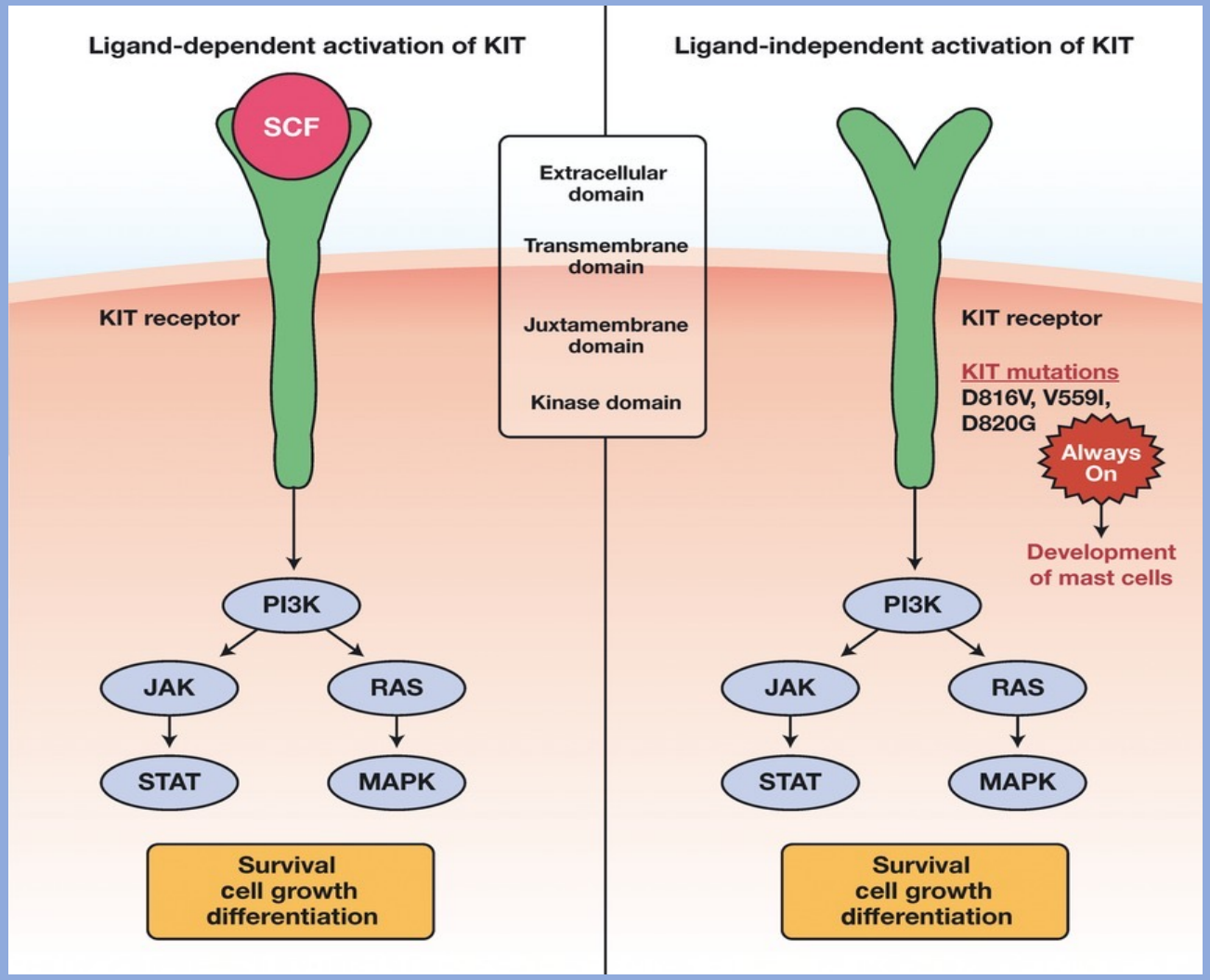


- Etiology unknown
  - c-kit mutation (exon 8,9, or 11)
    → gain of function
    → survival, proliferation, and oncogenic transformation of MCTs

**Not found in all MCTs

Etiology/Signalment

Mast Cell Tumors



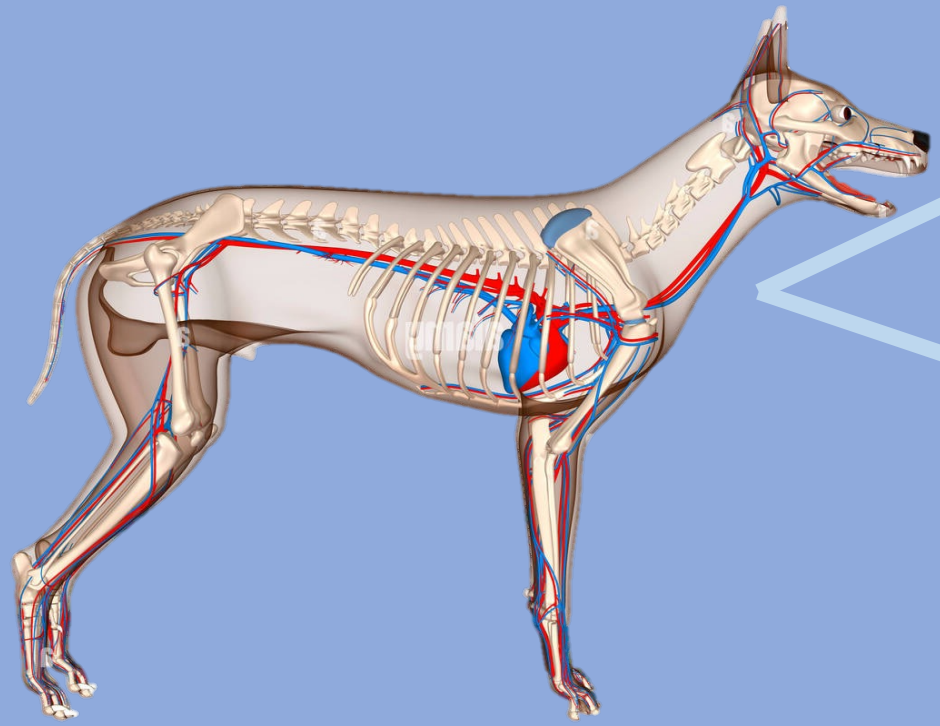
Stem cell factor (also known as SCF, KIT-ligand, KL, or steel factor)

- **Cytokine**
- **Binds KIT receptor tyrosine kinase (aka CD117), which is encoded by c-kit gene**

Mutations causing constitutive activation of KIT in the absence of ligand binding lead to uncontrolled mast cell proliferation, differentiation, and survival

Etiology/Signalment

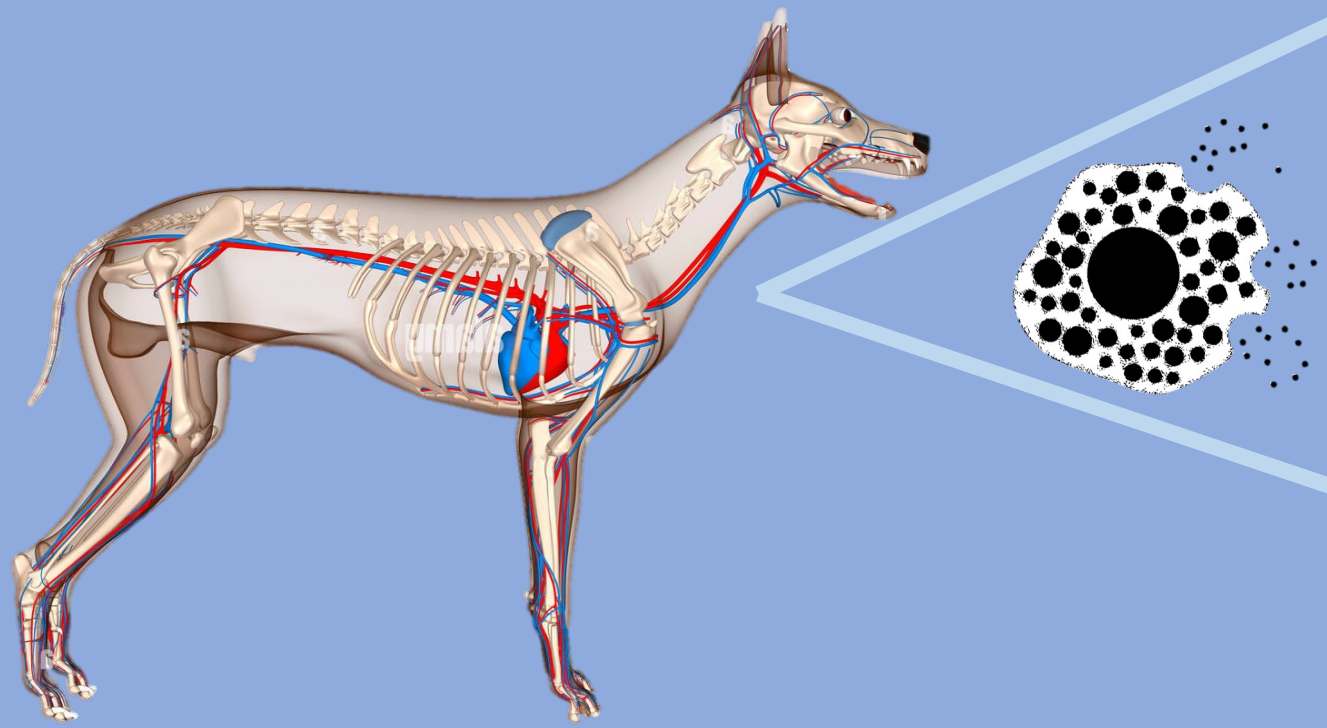
Mast Cell Tumors



- **Mean age: 8-9 yo**
- **Breeds: bulldog descendants, Labs, goldens, cockers, schnauzers, Staffordshire bull terriers, beagles, Rhodesians, Weimaraners, *shar peis***

Clinical Signs

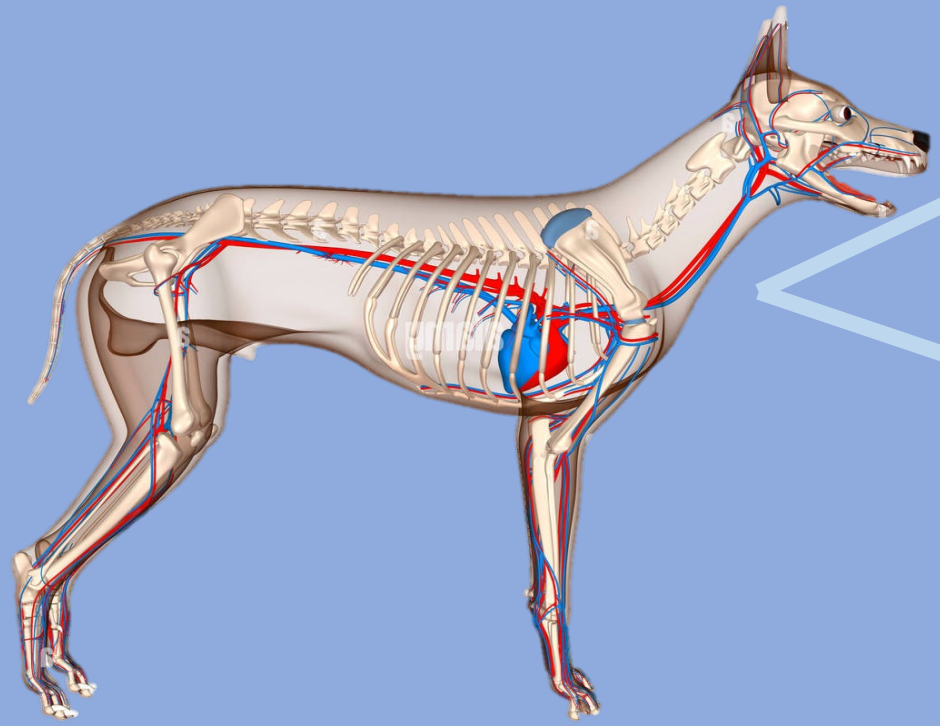
Mast Cell Tumors



- Single or multiple nodules (dermal, SQ)
- +/- ulceration, local swelling, erythema
- Trunk/perineum (50%) > limbs (40%) > head/neck (10%)

Clinical Signs

Mast Cell Tumors



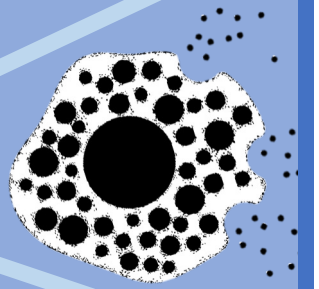
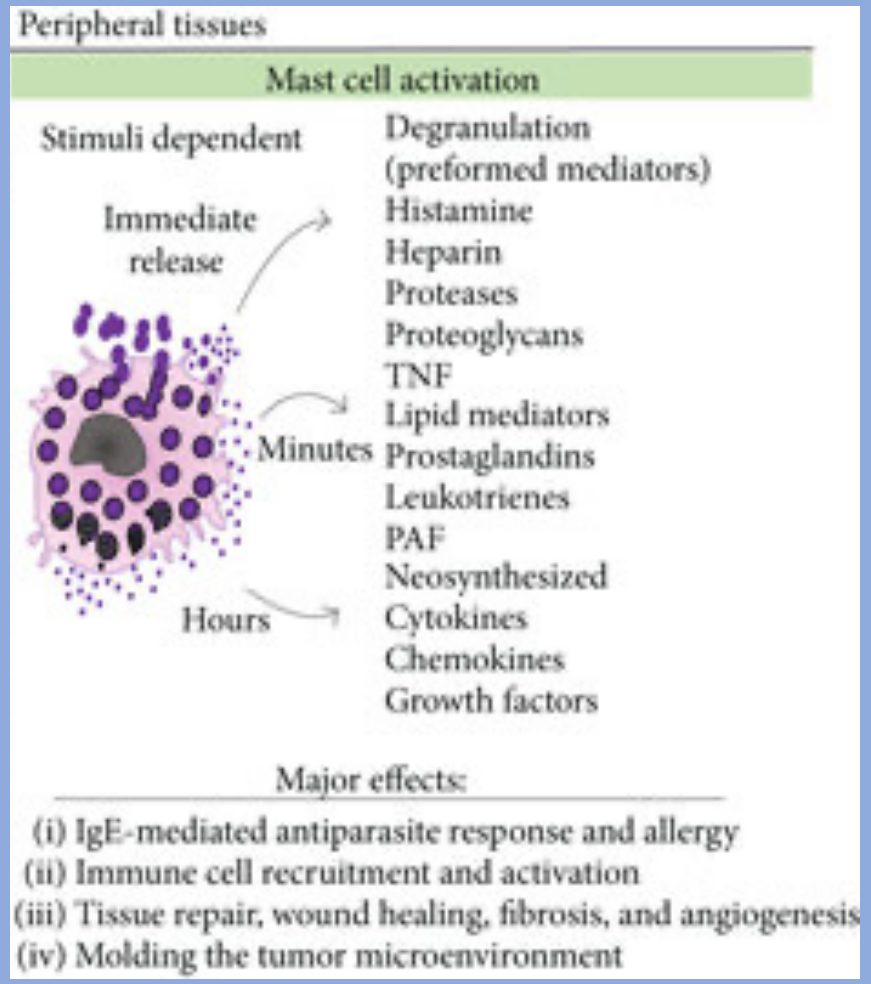


Figure 1: Clinical findings in a dog with a cutaneous non-nodular high grade MCT. The lesions at the time of the original presentation appeared as erythematous slightly raised plaques on the skin of the left thoracic wall.

Mast Cell Tumors



PARANEOPLASTIC

- **Darier's Sign: histamine**
- **GI ulceration: histamine → parietal cells**
- **Coagulation abnormalities: heparin**
- **Delayed wound healing/Wound dehiscence: vasoactive amines, proteolytic enzymes**
- **Hypereosinophilia: IL-5**
- **Hypotension: histamine, vasoactive substances, and maybe prostaglandin D series -> vasodilation**
- **Neovascularization and fibroblast proliferation: fibroblast growth factors**

Prognostic Indicators

Mast Cell Tumors

HISTOLOGIC GRADE

- Most strongly predictive of outcome
- Patnaik (3-tiered) vs. Kiupel (2-tiered)

**Not for SQ tumors

Prognosis (Patnaik)

Mast Cell Tumors

Grade I

- Well-differentiated
- Rare to spread beyond skin
- Surgery curative

Grade II

- Intermediately differentiated
- Unpredictable
- Mitotic index, AgNOR, and c-kit help prognosticate?

80-90% of Grade I and 75% of Grade II experience long-term survival after complete sx excision.

**A small % may still cause death

Prognosis (Patnaik)

Mast Cell Tumors

Grade I

- Well-differentiated
- Rare to spread beyond skin
- Surgery curative

Grade II

- Intermediately differentiated
- Unpredictable
- Mitotic index, AgNOR, and c-kit help prognosticate?

80-90% of Grade I and 75% of Grade II experience long-term survival after complete sx excision.

**A small % may still cause death

Grade III

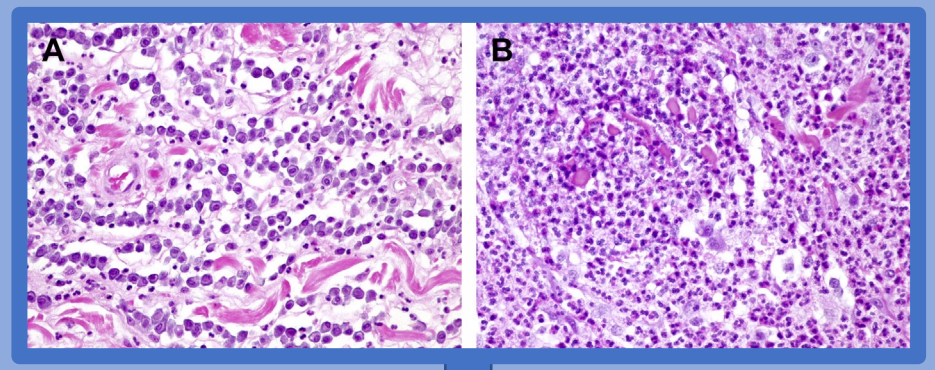
- Poorly differentiated
- Invasive, aggressive
- Mets to spleen, bone marrow, liver, lnn (rarely lung)
- Surgery alone unlikely to control disease

55-96% are metastatic
MST <1 year

Prognosis (Kiupel)

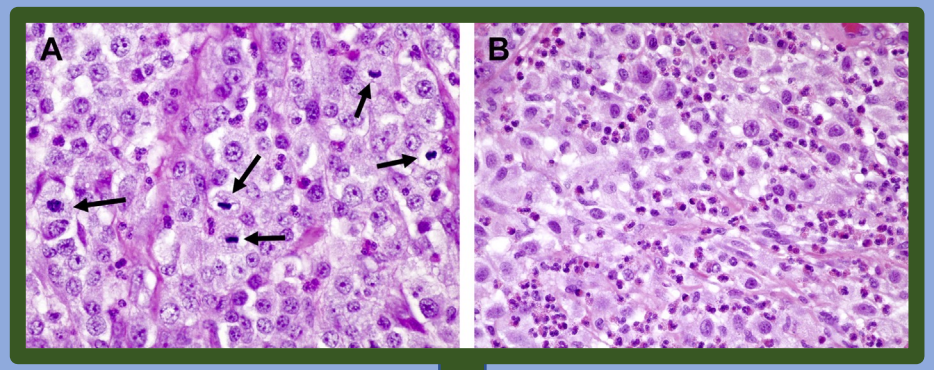
Mast Cell Tumors

Low Grade



- MST > 2 years

High Grade



- MST <4 months
- Shorter time to metastasis or new tumor development

https://doi.org/10.1016/j.cvsm.2019.04.002

Prognostic Indicators

Mast Cell Tumors

Subcutaneous Mast Cell Tumors

- Restricted to the subcutis only
- Low incidence of aggressive behavior
- No validated histopathologic grading system

Other Prognostic Indicators

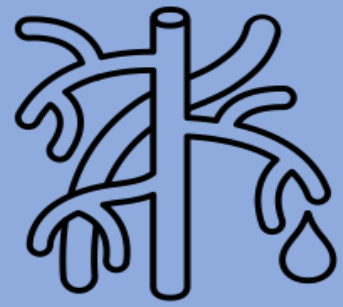
Mast Cell Tumors

Cytology (granularity)

Mitotic index, AgNOR, KI-67

c-kit mutations (exon 11)

Breed



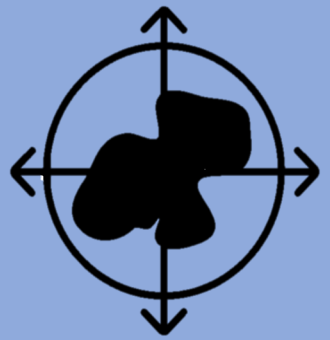
Microvessel density

Tumor growth rate

- Oral
- Mucosa
- Prepuce
- Scrotum
- Bone marrow
- Viscera
- Subungual

Lesion distribution

DNA CNV



Tumor size

Age

Tumor recurrence

Prognostic Indicators

Mast Cell Tumors

c-kit mutations

- Alterations in the oncogene (c-kit) are associated with:
  - 25-30% intermediate and high grade MCTs
  - Mutation in exon 11 - increased risk of local recurrence, metastasis, and tumor-related death

Diagnostic Algorithm

Mast Cell Tumors

FNA of mass

Anatomic site amenable to wide surgical excision?

Yes

Negative prognostic factors present?

No

Complete margins, intermediate to low grade, no negative prognostic factors

Routine follow up: 1 month, then q3 months for 1.5 years, then q6 months. Physical + lymph node exams.

Diagnostic Algorithm

Mast Cell Tumors

FNA of mass

Anatomic site amenable to wide surgical excision?

No

Expand diagnostics before definitive therapy

Yes

Negative prognostic factors present?

Yes

Incomplete margins,
Poorly differentiated,
Highly proliferative

No

Complete margins, intermediate to low grade, no negative prognostic factors

Routine follow up: 1 month, then q3 months for 1.5 years, then q6 months. Physical + lymph node exams.

Diagnostic Algorithm

Mast Cell Tumors

FNA of mass

Anatomic site amenable to wide surgical excision?

No

Expand diagnostics before definitive therapy

Yes

Negative prognostic factors present?

Yes

Incomplete margins,
Poorly differentiated
Highly proliferative

LNN

Histopath

AUS

CBC/Chem

No

Complete margins, intermediate to low grade, no negative prognostic factors

Spleen/liver aspirate

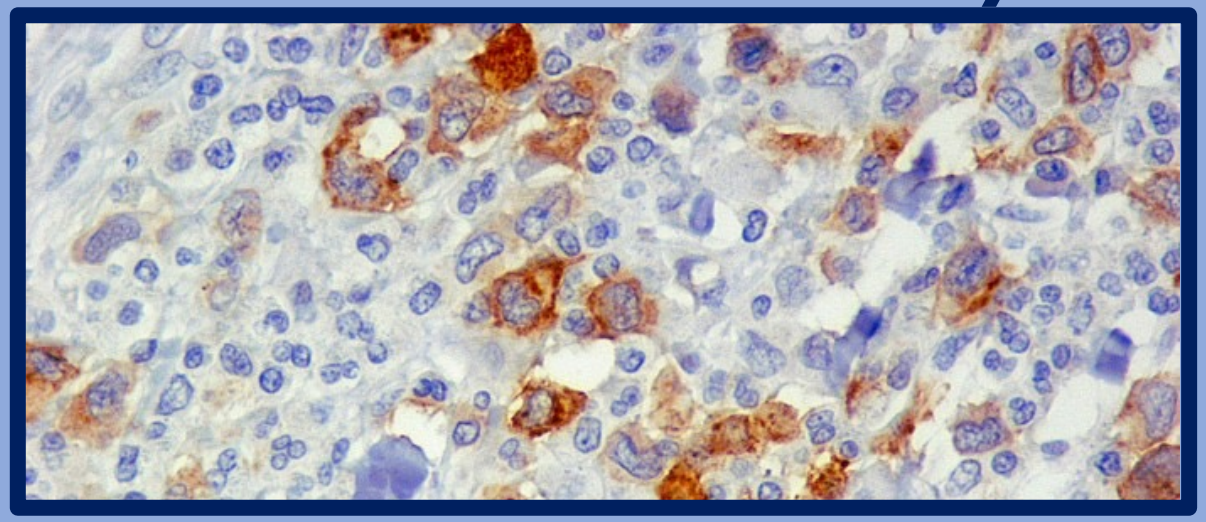
+/-

KIT analysis

Routine follow up: 1 month, then q3 months for 1.5 years, then q6 months. Physical + lymph node exams.

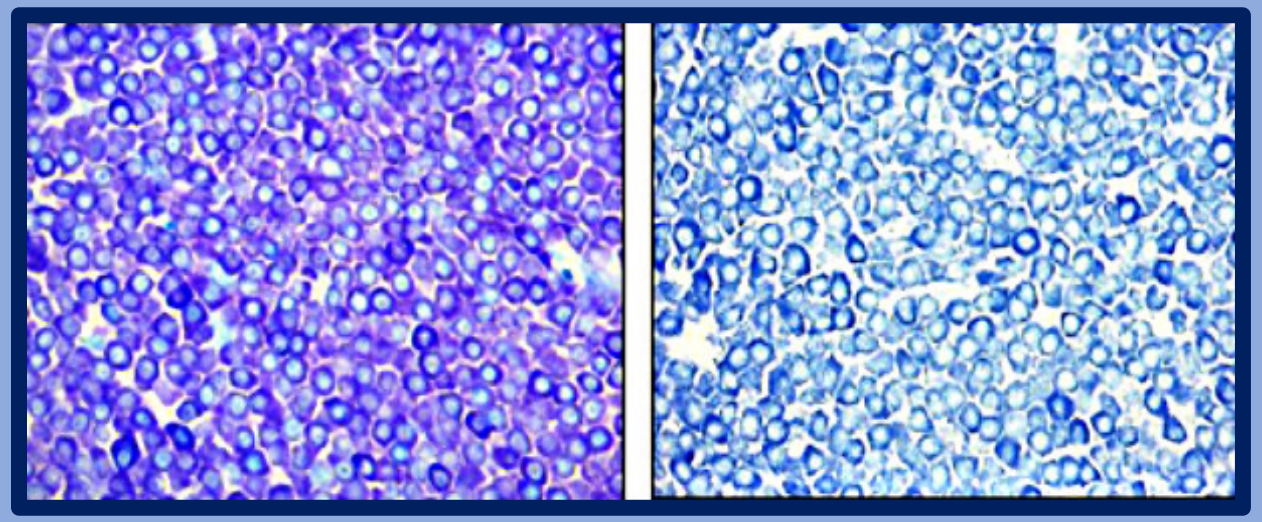
Mast Cells

Immunohistochemistry



- Vimentin+
- KIT(CD117)+
- Tryptase+
- Chymase+
- MCP-1+
- IL-8+

Stains



- Toluidine blue
- Giemsa

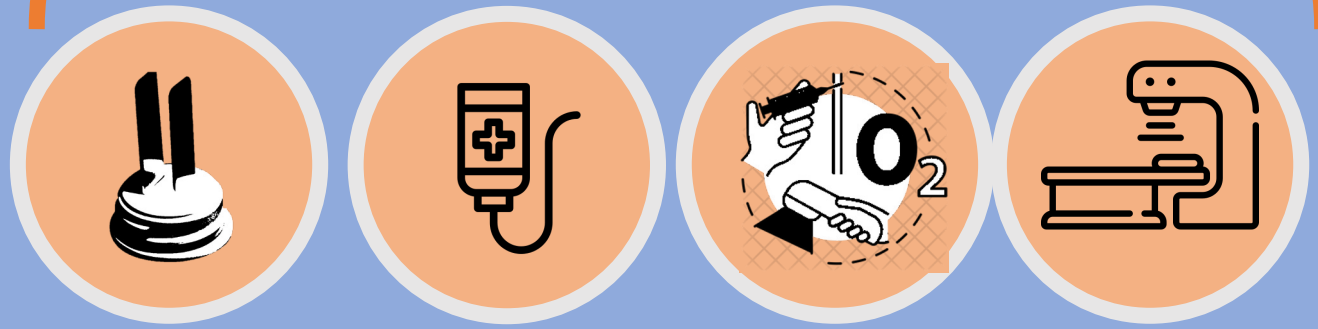
Treatment

Mast Cell Tumors

Ablative Therapy

Wide surgical excision is treatment of choice

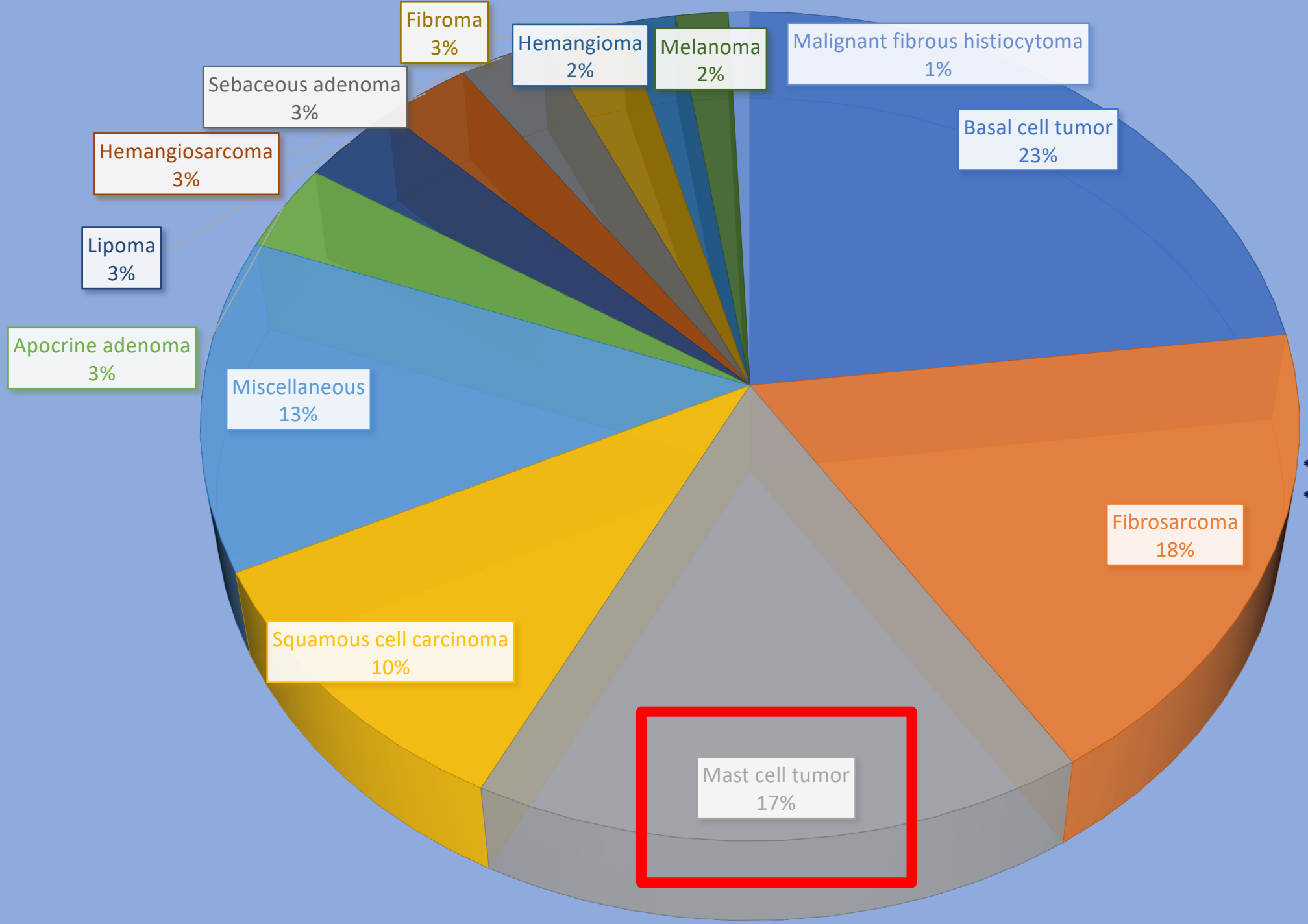
Cytotoxic Therapy



Supportive Care

Combat sequelae of mast cell degranulation:

1. Antihistamines
2. Antacids
3. GI protectants



CATS

*4 worldwide studies

*1200 tumors

Etiology/Signalment

Mast Cell Tumors

- 3 mast cell tumor syndromes in cats:
  1. Cutaneous
  2. Splenic/visceral
  3. Intestinal

Etiology/Signalment

Mast Cell Tumors

Concurrent visceral and skin mast cell tumors are generally considered to be two distinct, independent forms of mast cell neoplasia

- **3 mast cell tumor syndromes in cats:**
  1. **Cutaneous**
  2. **Splenic/visceral**
  3. **Intestinal**

Etiology/Signalment

Mast Cell Tumors

- **2 cutaneous mast cell tumor types:**
  1. **Histiocytic**
  2. **Mastocytic**

***In both types, cats are usually systemically healthy**

Etiology/Signalment

Mast Cell Tumors

- Etiology: unknown
  - Some have activating c-kit mutations
- Mean age:
  - Mastocytic type: 8-9 yo
  - Histiocytic type: ~2 yo
- Breed: Siamese (histiocytic)

Clinical Signs

Mast Cell Tumors

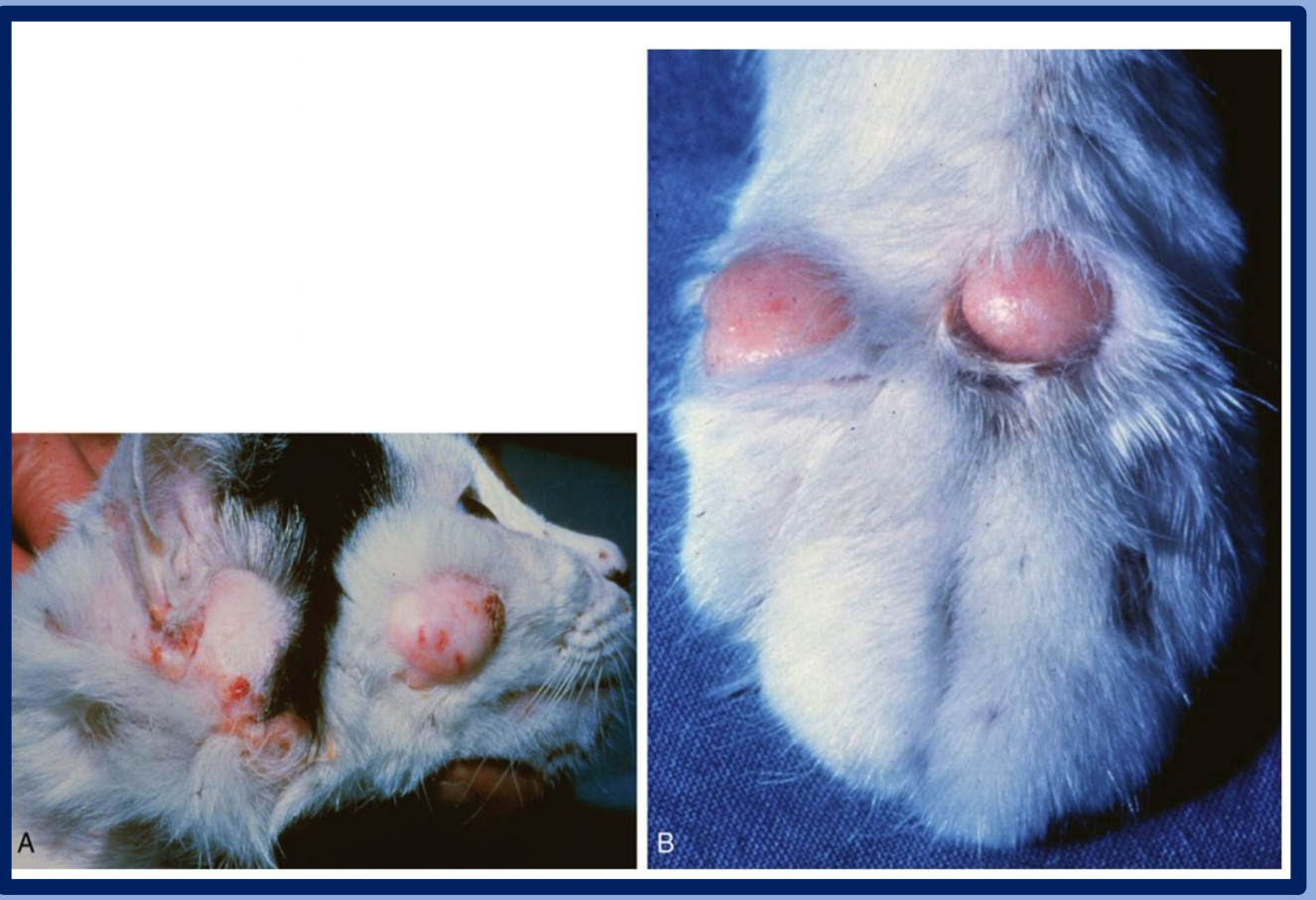
HISTIOCYTIC SUBTYPE

- Siamese cats
- Predominantly young
- Less common than mastocytic

- Multiple, firm, non-pruritic, hairless, pink, SQ nodules

Clinical Signs

Mast Cell Tumors



MASTOCYTIC SUBTYPE

- More common
- Older cats
- Head, neck > trunk, limbs, mouth

- Different presentations
  - Solitary, raised, firm, well-circumscribed, hairless, white-pink (most common)
  - +/- Multiple nodules (20%)
  - SQ nodules (ddx panniculitis)
  - +/- Darier's sign

Prognostic Indicators

Mast Cell Tumors

No one factor is entirely predictive of biologic behavior in cats

Usually more benign than in dogs

Prognostic Indicators

Mast Cell Tumors

- **No histopath grading system**
- **Higher mitotic index generally indicates higher risk for metastasis and local recurrence (*but not always*)**
- **>5 tumors = worse prognosis**
- **Mastocytic type**
  - **Compact vs. anaplastic**

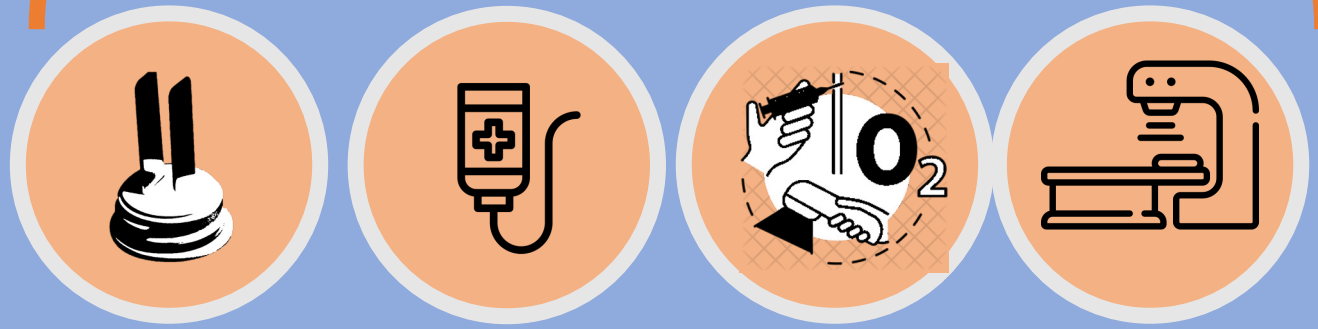
Treatment

Mast Cell Tumors

Ablative Therapy

Treatment of choice
Wide margins not as critical

Cytotoxic Therapy



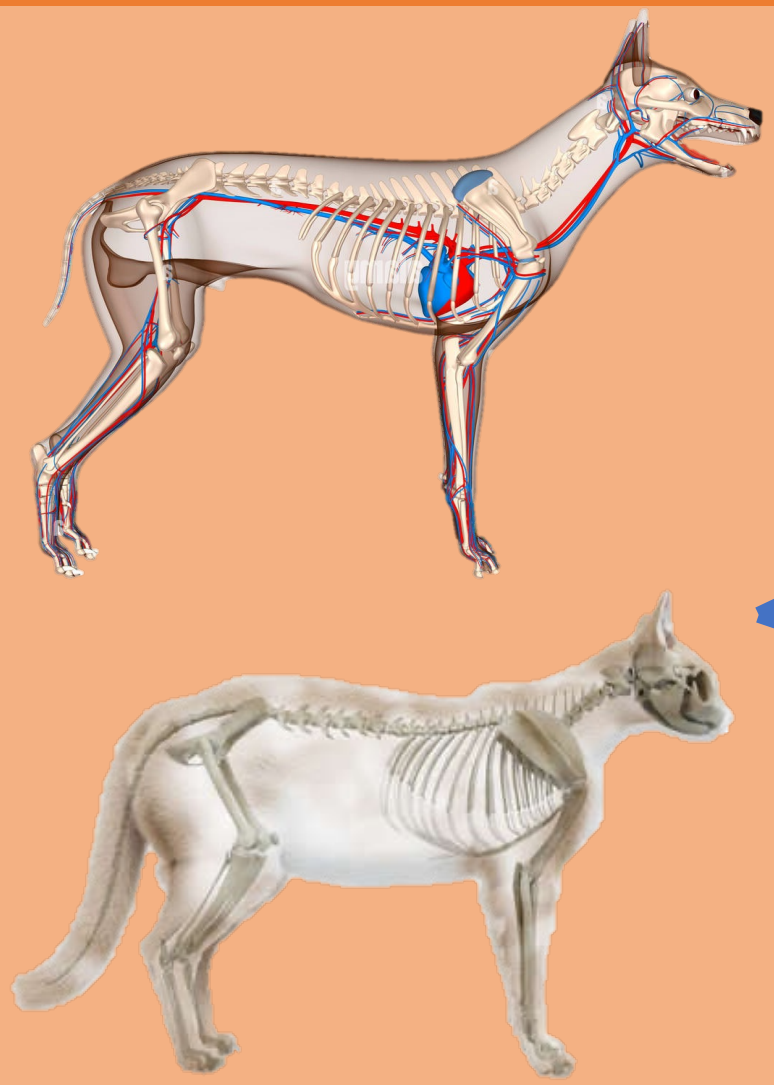
Supportive Care

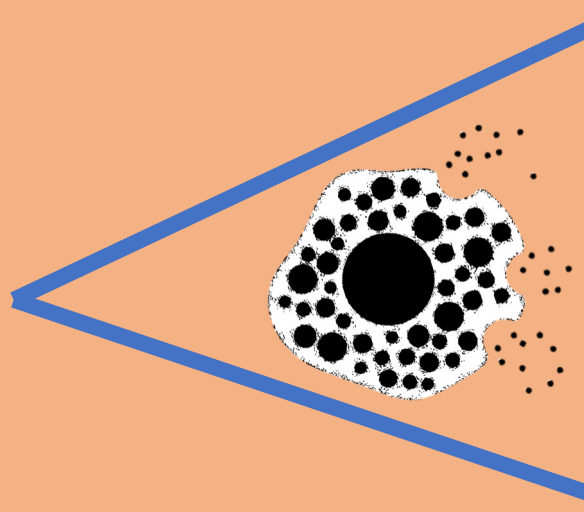
Same as dog

Spontaneous regression of histiocytic form is possible

Etiology/Signalment

Urticaria Pigmentosa



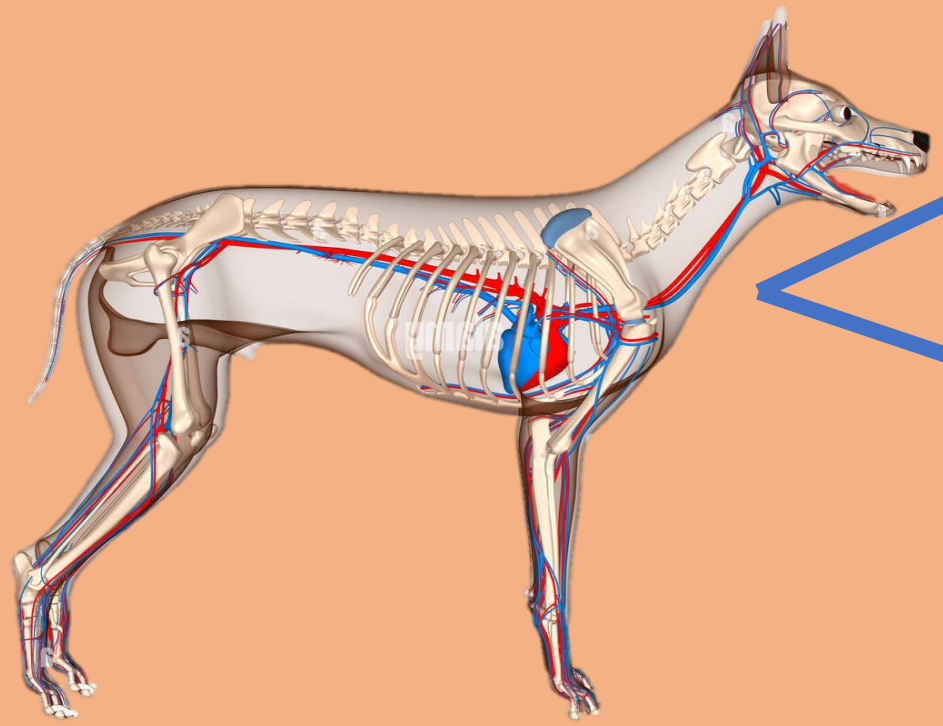


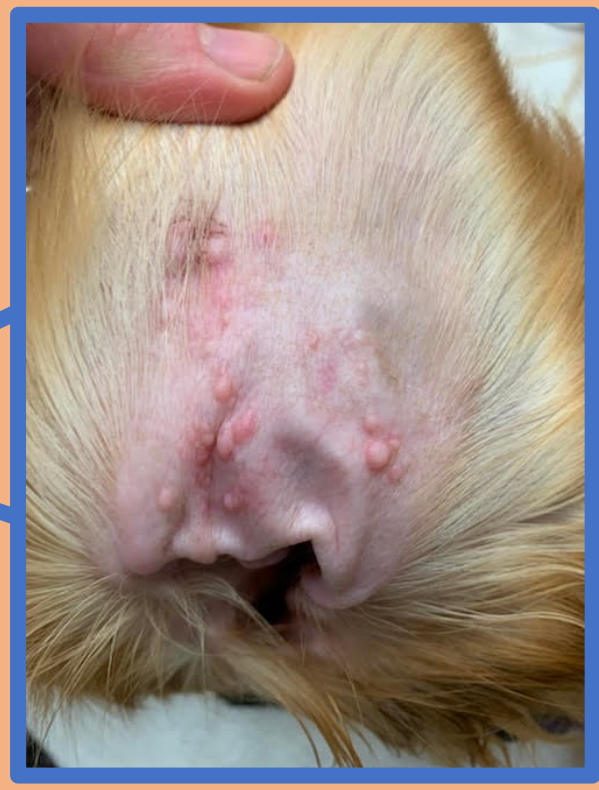
Differentiation from MCTs historically has been based on:

- **number of lesions (MCT are typically solitary, though they may be multifocal)**
- **age at onset (typically young)**
- **lack of progression (indolent mast cell behavior)**
- **restriction to skin**

Clinical Signs

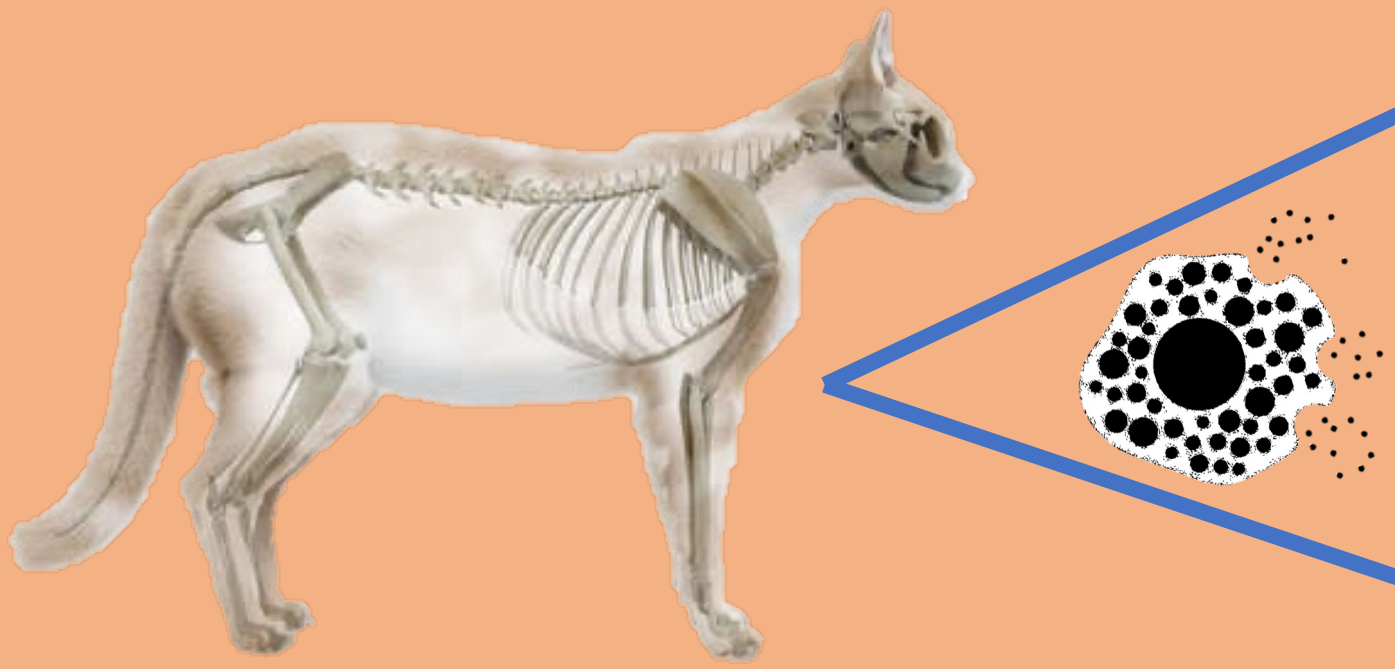
Urticaria Pigmentosa





Clinical Signs

Urticaria Pigmentosa



- Devon rex, sphynx

---

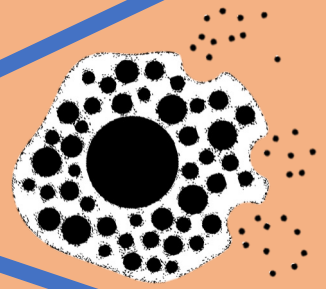
3 Clinical Presentations

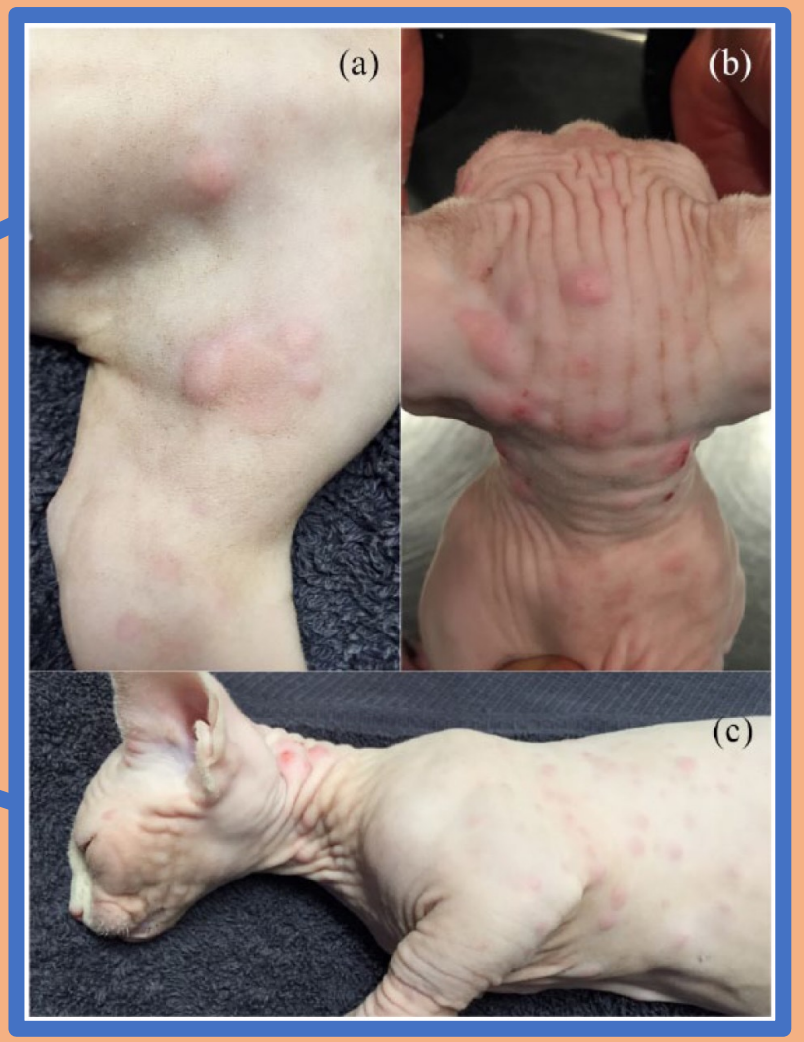
Clinical Signs

Urticaria Pigmentosa

1.

1. **Non-pigmented pruritic papules and wheals on head, shoulders, ventral neck, and axillae**

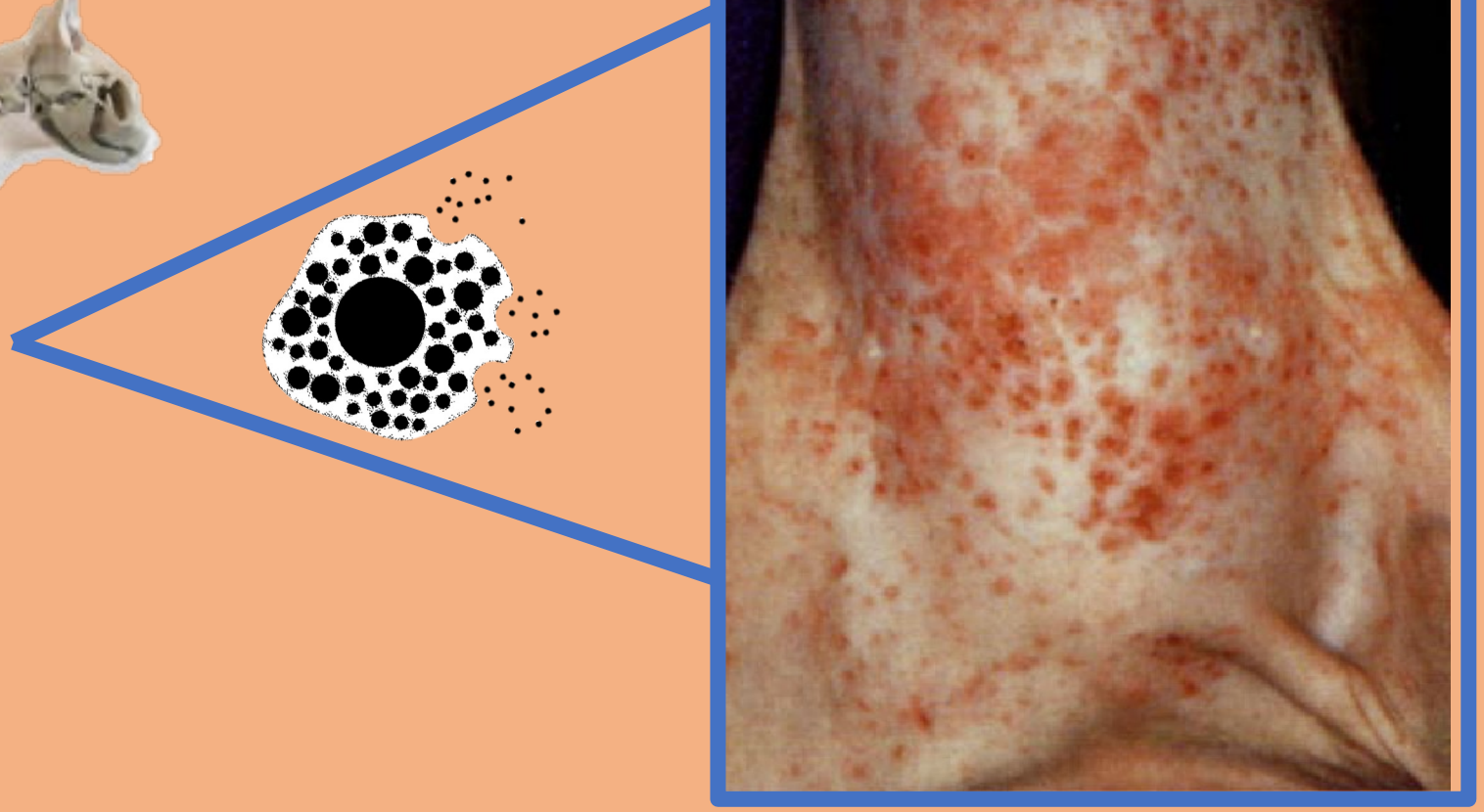




Clinical Signs

Urticaria Pigmentosa

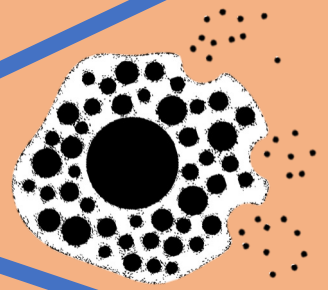
2. **Non-pigmented maculopapular erythematous and pruritic dermatitis with crusts**



Clinical Signs

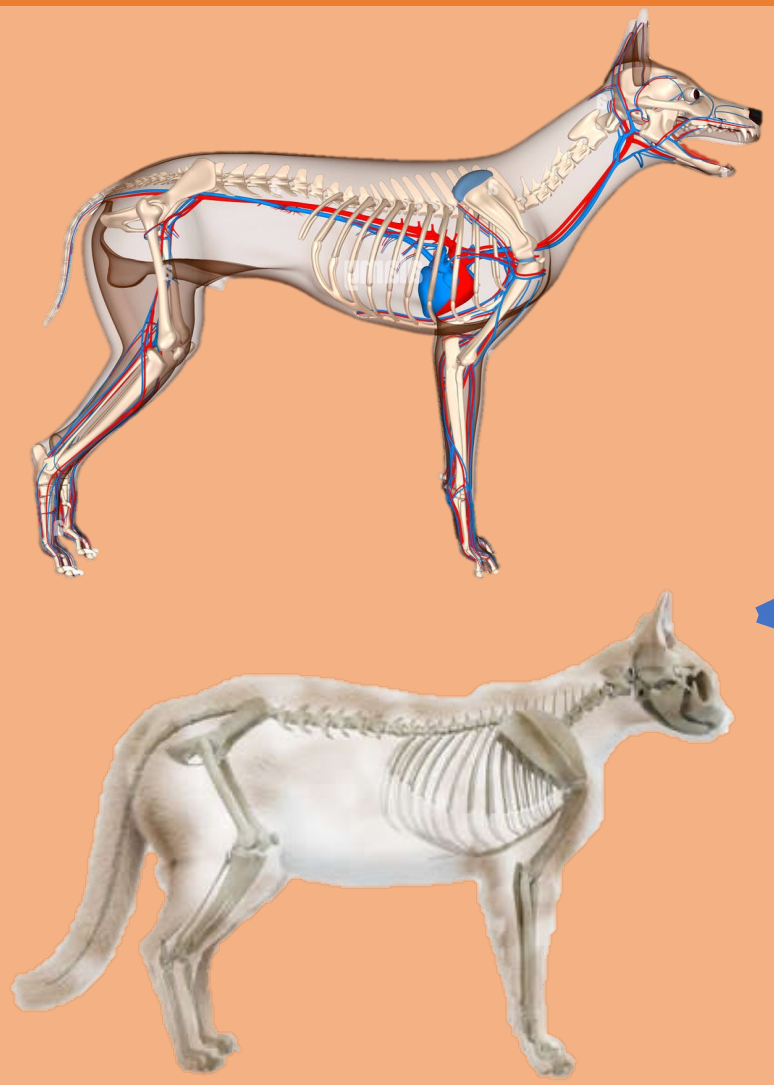
Urticaria Pigmentosa

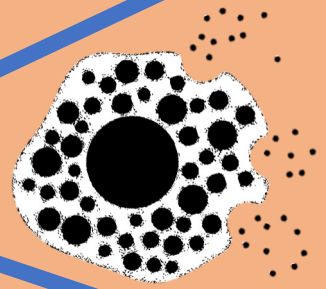
3. **Pruritic chronic dermatitis with bilaterally symmetrical pigmented lesions on flanks**



Treatment / Prognosis

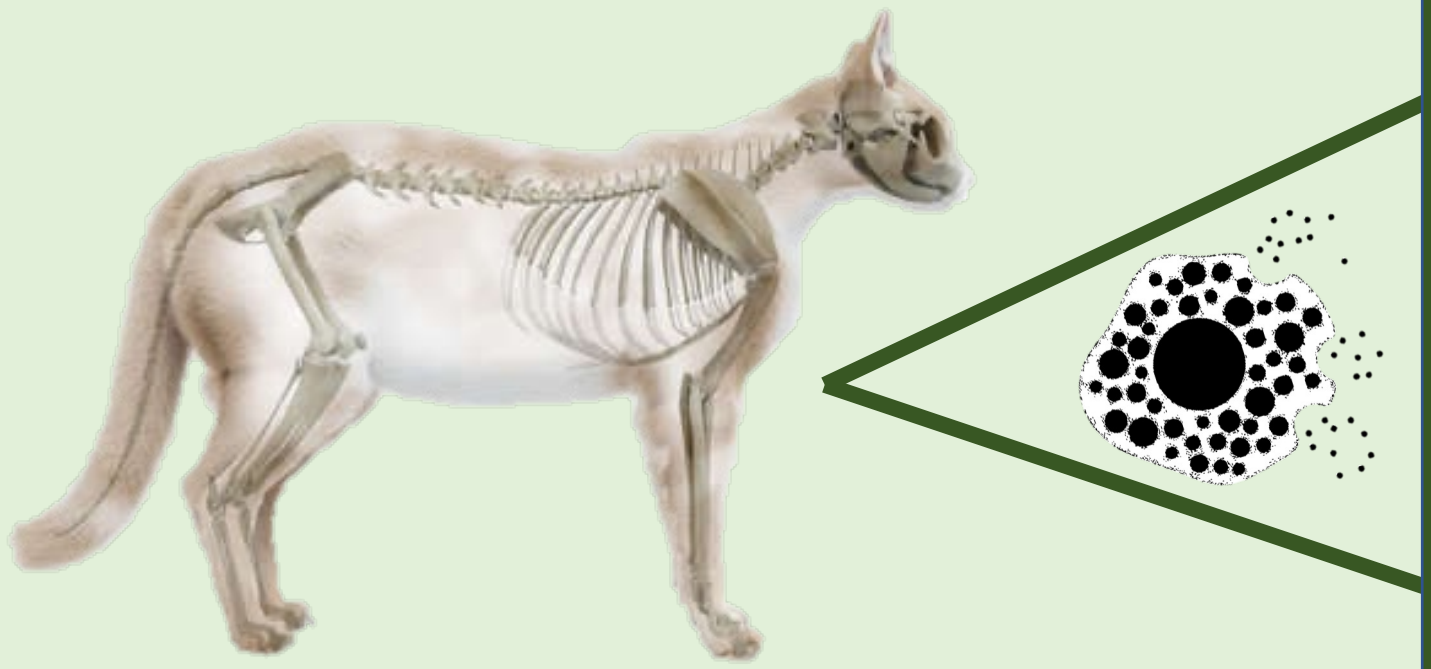
Urticaria Pigmentosa





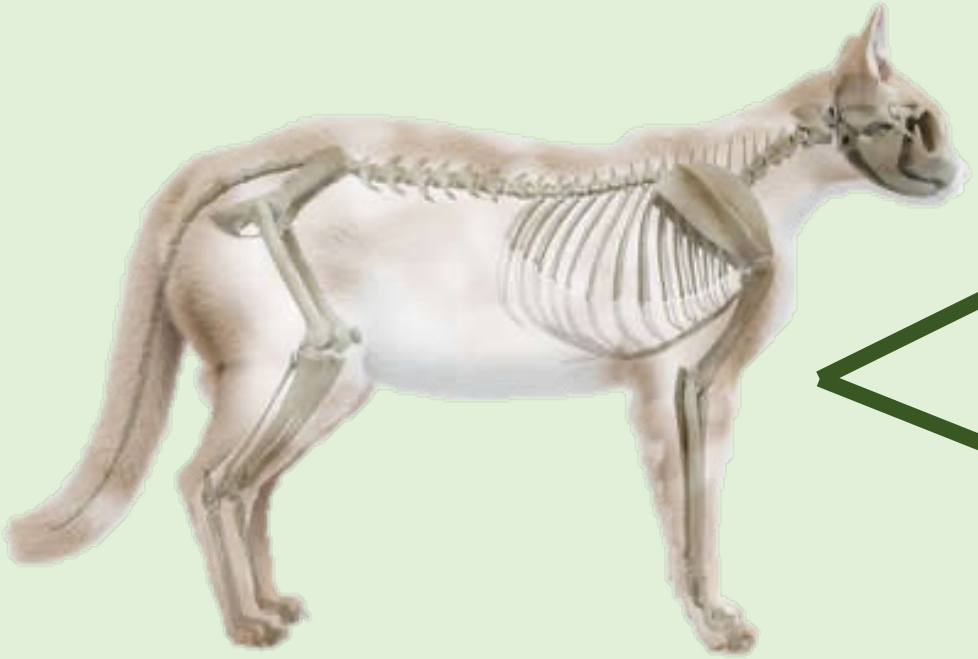
- <u>Treatment</u>: Variable response to oral steroids, H_1 and H_2 blockers. Cytopoint for pruritus (dogs).
- <u>Prognosis</u>: Excellent for long-term survival. Indolent progression. Spontaneous regression possible.

Diffuse Cutaneous Mastocytosis



- N=1 cat
- 1 yo FS DSH
- Pruritic papulocrustous lesions from head to whole body
- Diffuse induration / lichenification
- Lymph node involvment
- Poor response to treatment

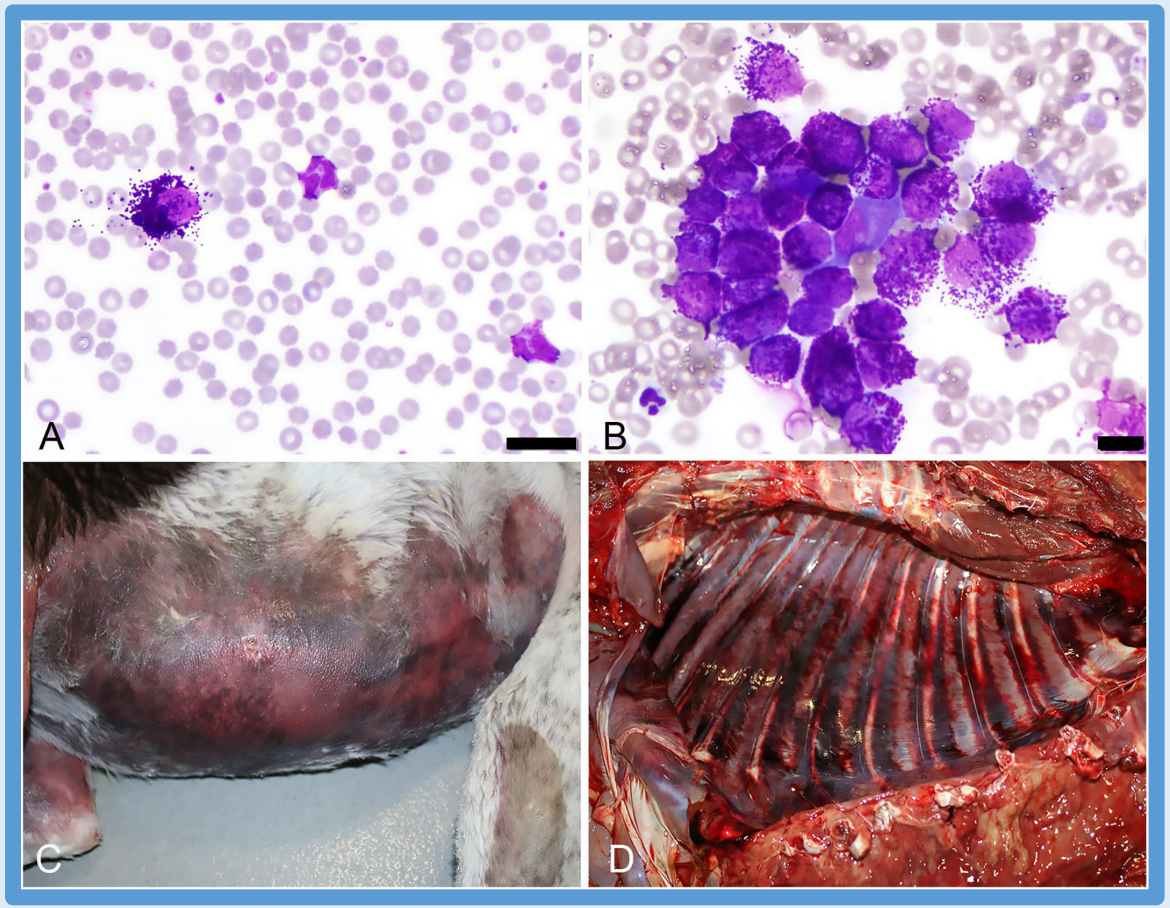
Diffuse Cutaneous Mastocytosis



Same as urticaria pigmentosa?

- **Not Sphynx/Devon Rex**
- **Diffuse lichenification**
- **Lymph node involvement**

Systemic Mastocytosis with Cutaneous Involvement

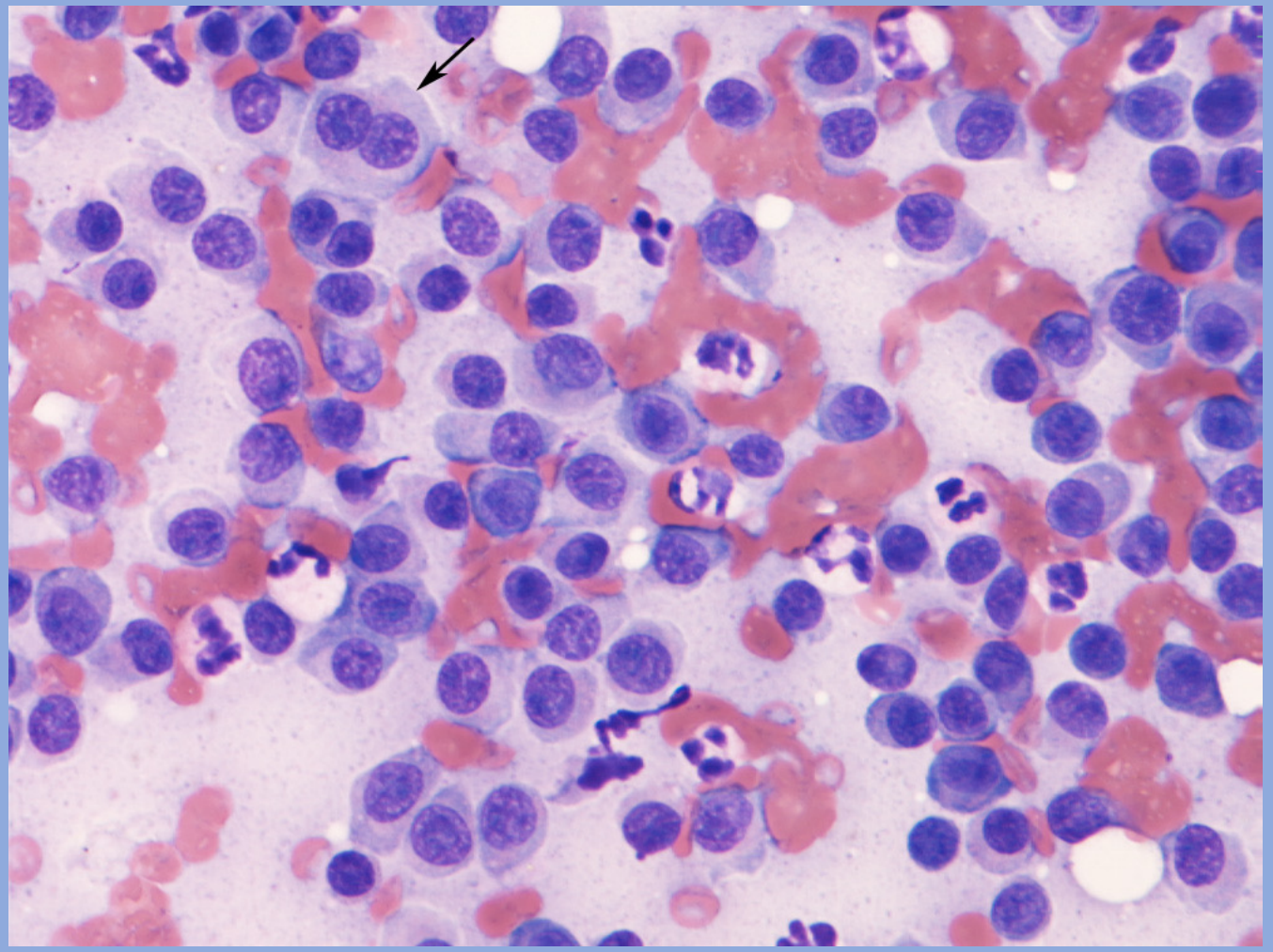


N=1, 5 yo FS Greyhound
Skin, liver, spleen, heart, esophagus, bone marrow
Ecchymoses, pitting edema

N=1, 15 yo F DMH
Skin, liver, spleen, bone marrow, lung

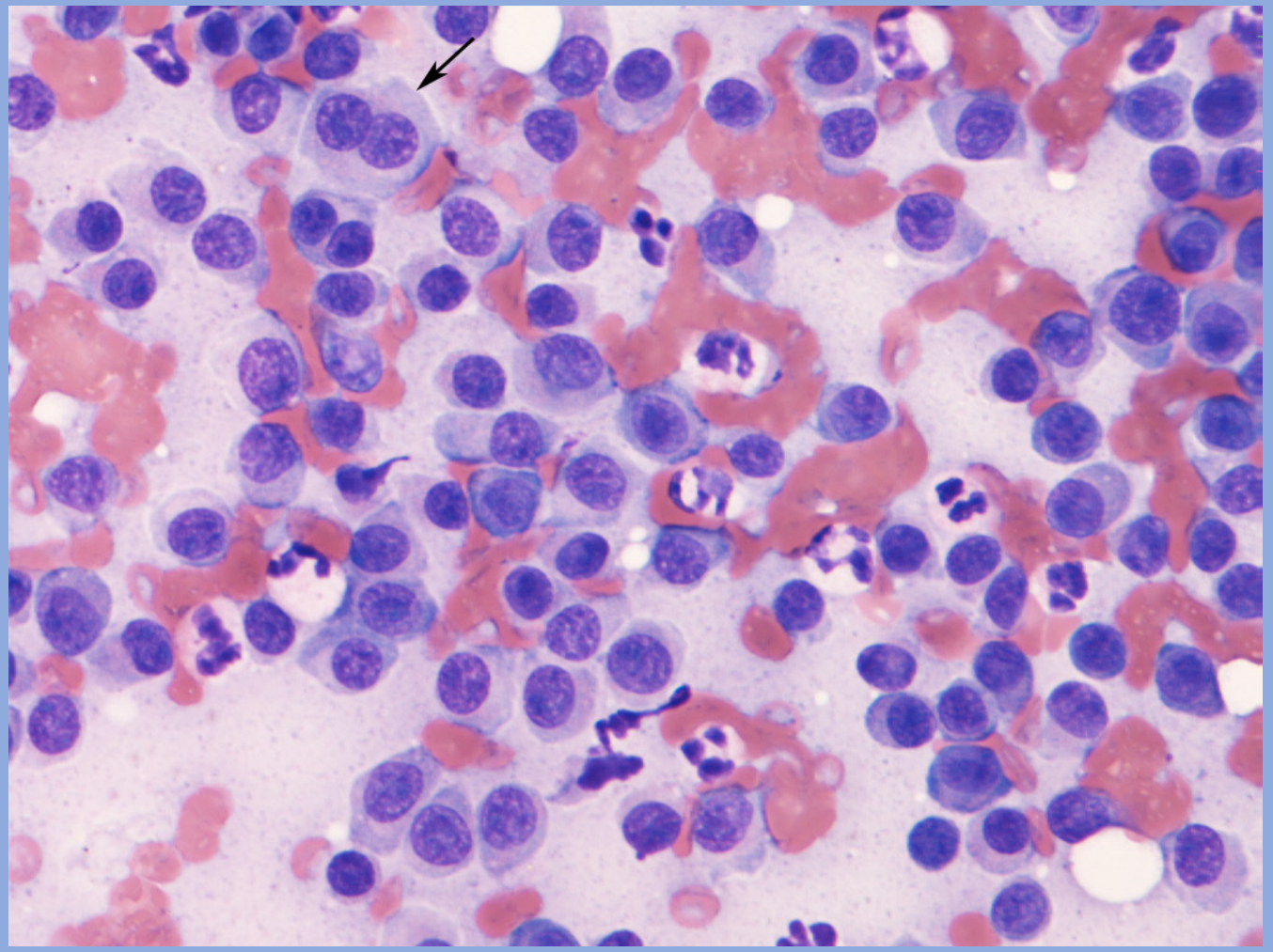
Case 3

Cytology



Diagnosis?

Cytology



Plasma cells

Cutaneous Plasma Cell Disorders

3 Types in Dogs and Cats

Solitary Extramedullary Cutaneous Plasmacytoma

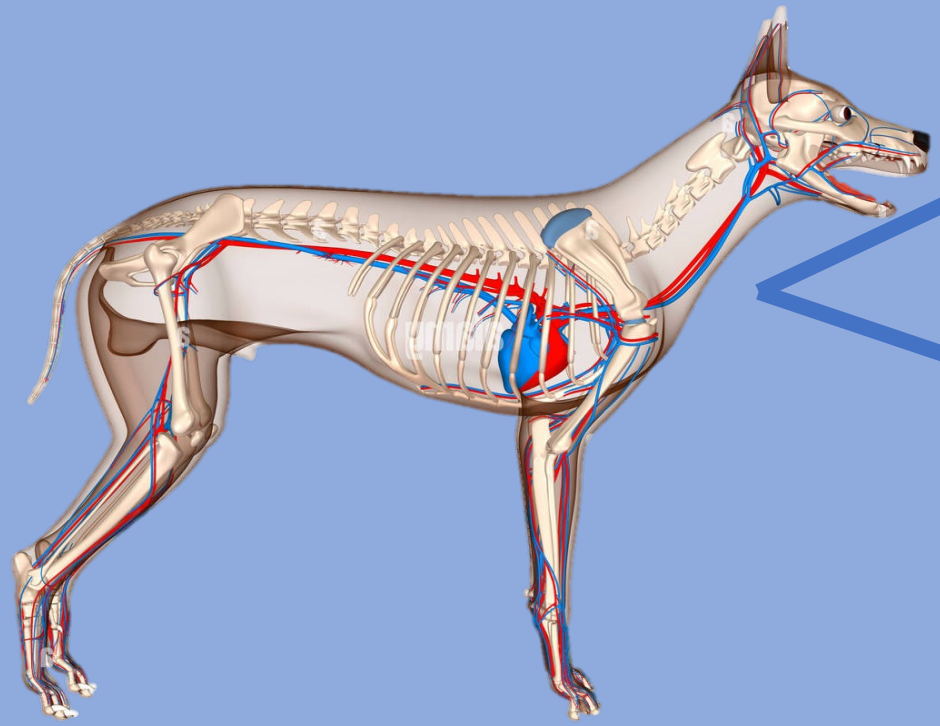
Cutaneous Plasmacytosis

Cutaneous Metastasis from Multiple Myeloma

95% cutaneous plasma cell tumors

Etiology/Signalment

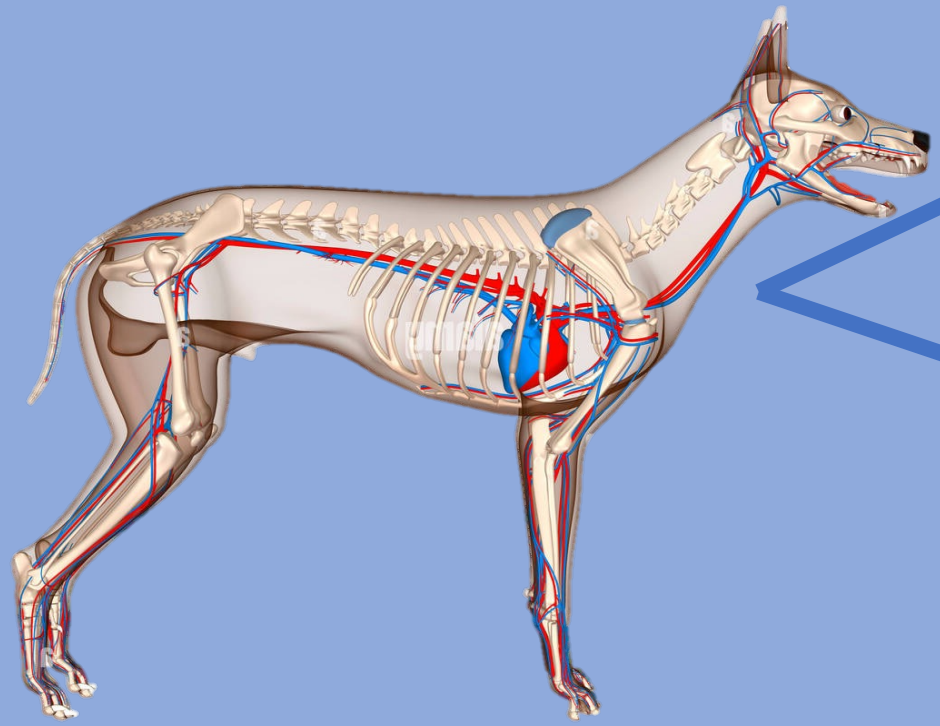
Solitary Extramedullary Cutaneous Plasmacytoma



- Extramedullary solitary plasmacytomas are ***mostly cutaneous*** (86%)
  - Also mouth, lips, GI tract, spleen, genitalia, eye, nictitans, larynx, liver, trachea

Etiology/Signalment

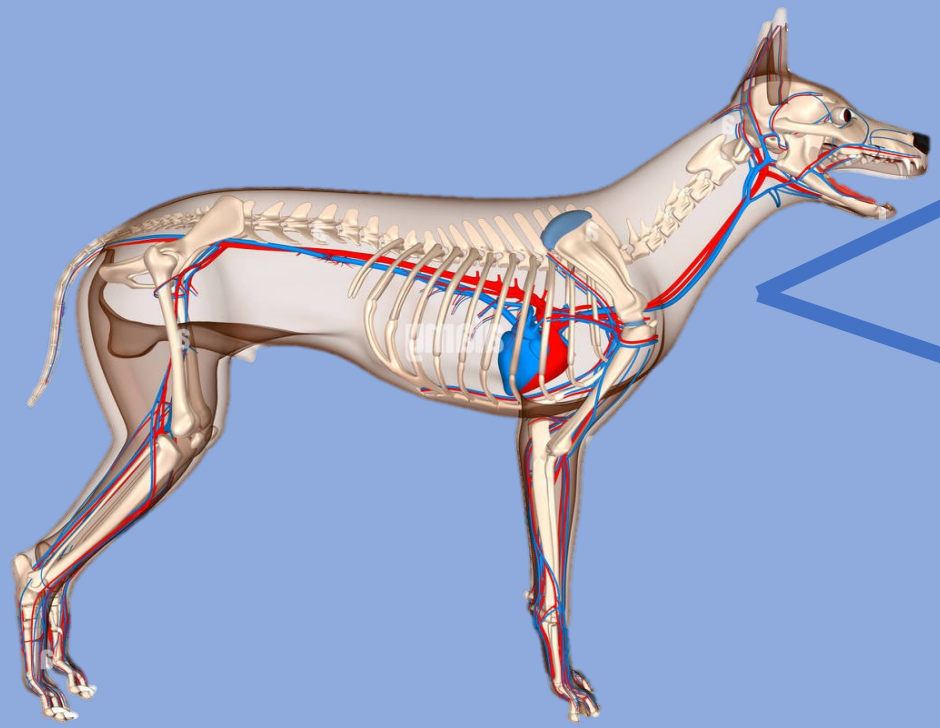
Solitary Extramedullary Cutaneous Plasmacytoma



- **Signalment:** Mean 9-10 yo
- Predisposed breed: Airedale, boxer, cocker spaniel, German shepherd dog, West Highland white terrier, Yorkshire terrier

Clinical Signs

Solitary Extramedullary Cutaneous Plasmacytoma



- Single, solitary, smooth, raised pink, variably alopecic nodule up to 10cm diameter

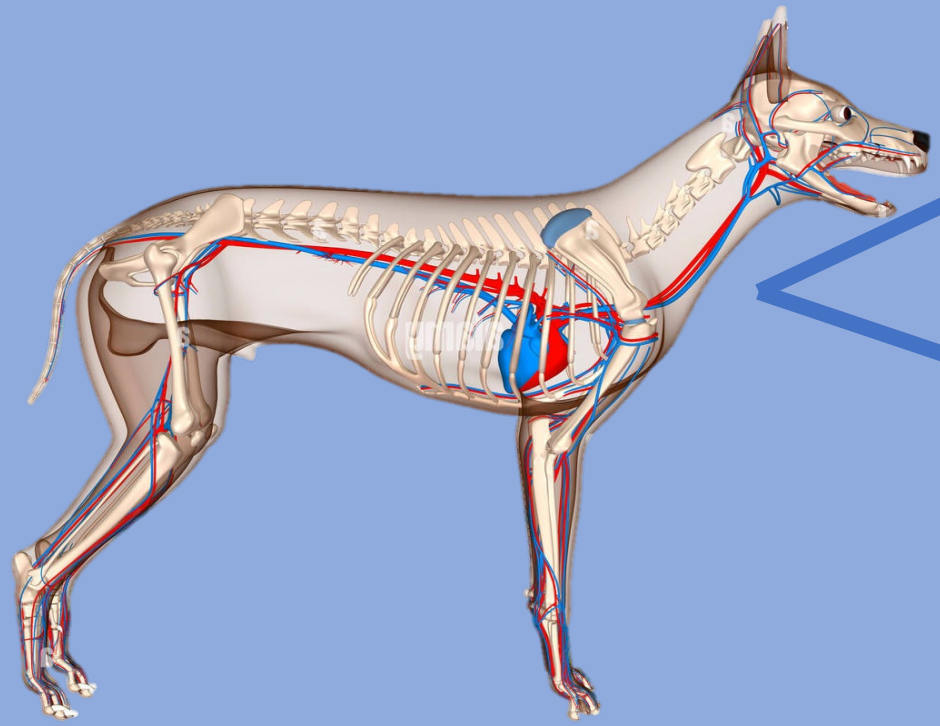
---

SYSTEMIC SIGNS

- Typically none

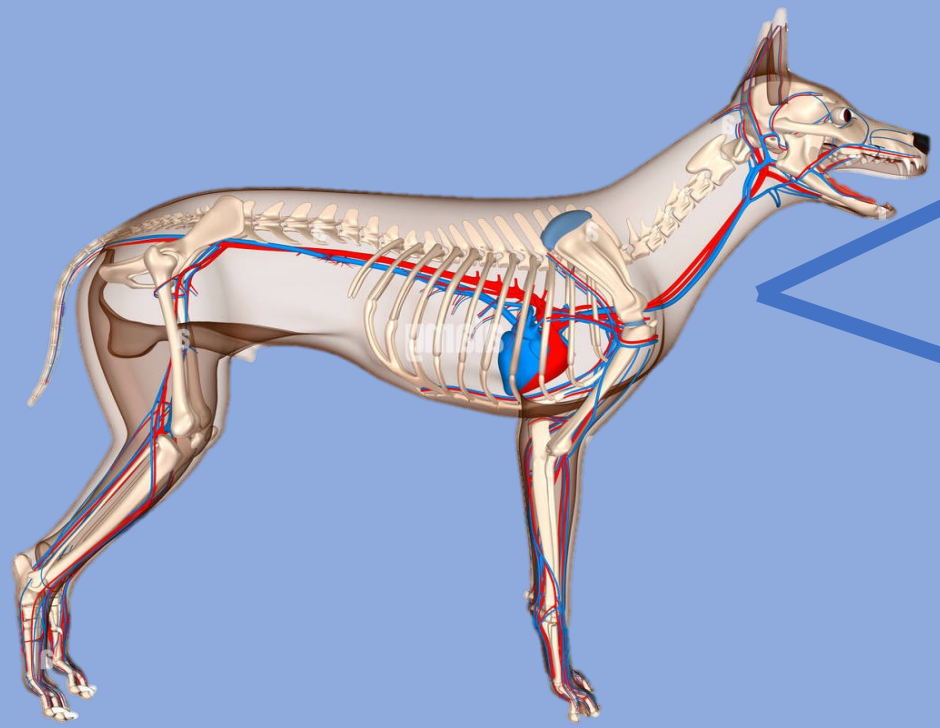
Clinical Signs

Solitary Extramedullary Cutaneous Plasmacytoma



Treatment/Prognosis

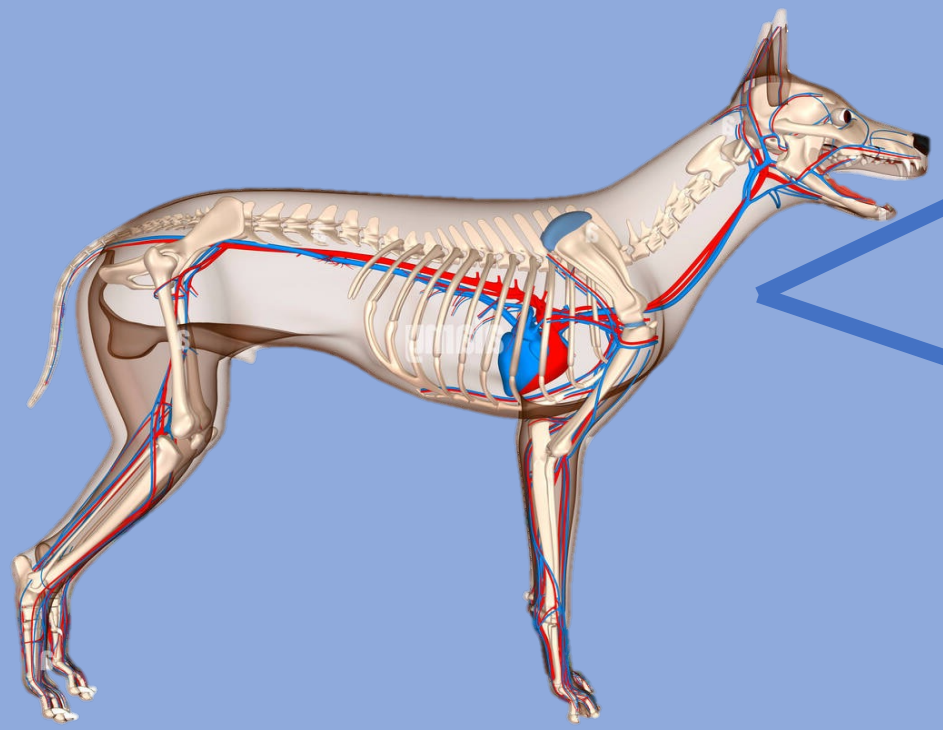
Solitary Extramedullary Cutaneous Plasmacytoma



- Treatment: Conservative sx excision typically curative. Anecdotally: cryo, CO_2 laser, electrocautery
- Prognosis: Vast majority are BENIGN and amenable to local therapy, even if vascular invasion on histopath.
  - Typically, no effect on lifespan

Treatment/Prognosis

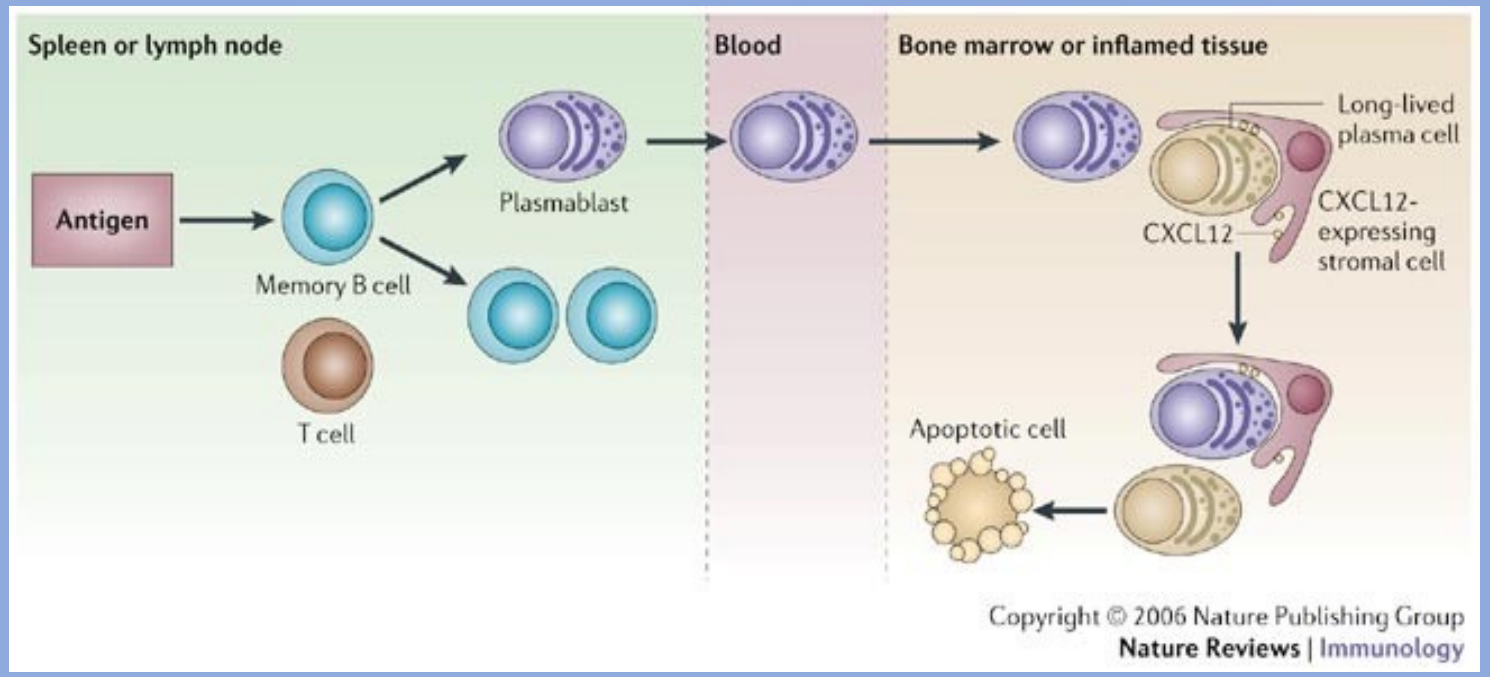
Solitary Extramedullary Cutaneous Plasmacytoma



HOWEVER....

- Local recurrence 5% after sx
- 2% develop nodal or distant metastases
- <2% develop new cutaneous plasmacytomas at distant sites
- Monoclonal gammopathy or plasma cell leukemia possible

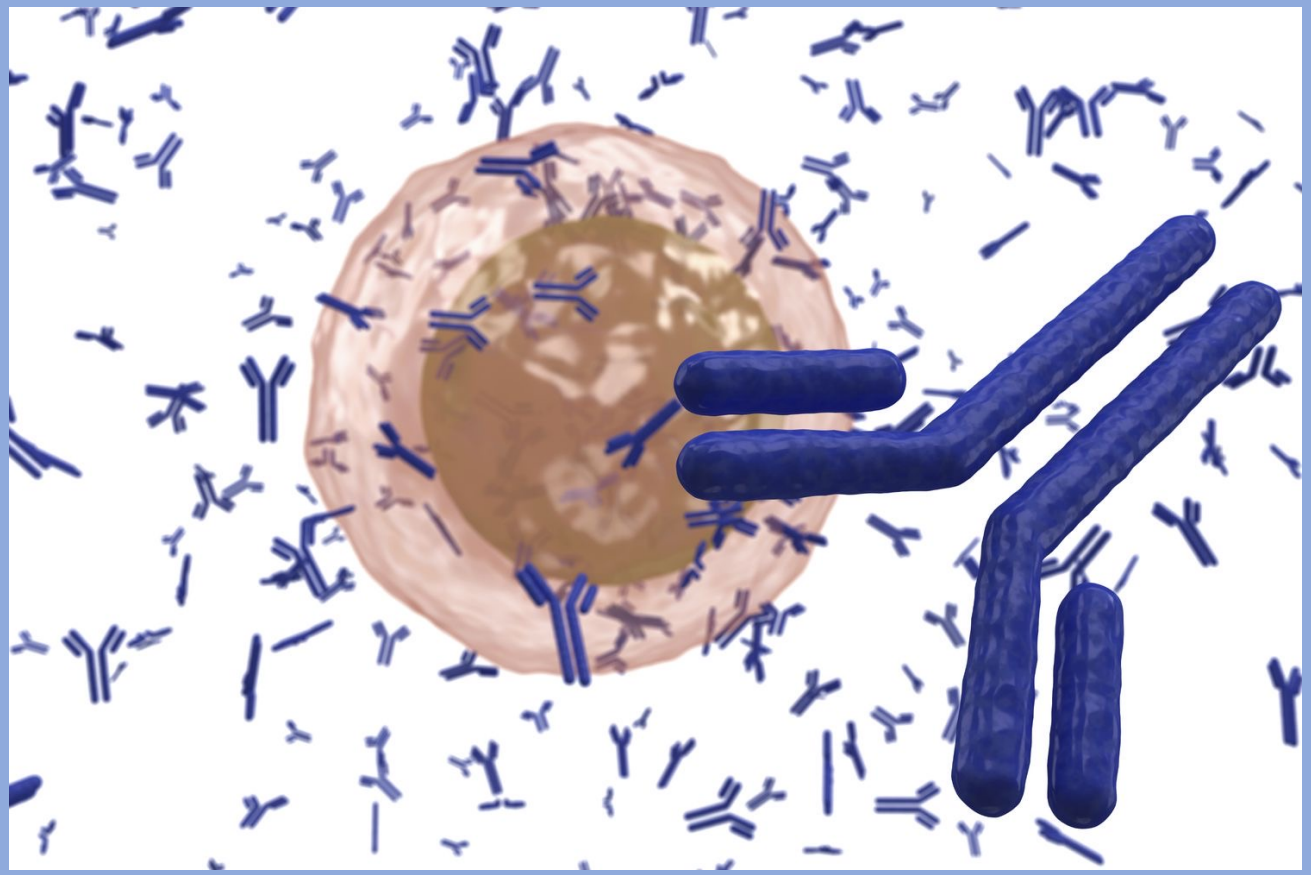
Plasma Cell



Plasma cell (plasmacyte);

Immune cell that develops from activated B-cells for the purpose of synthesizing and secreting a specific type of antibody

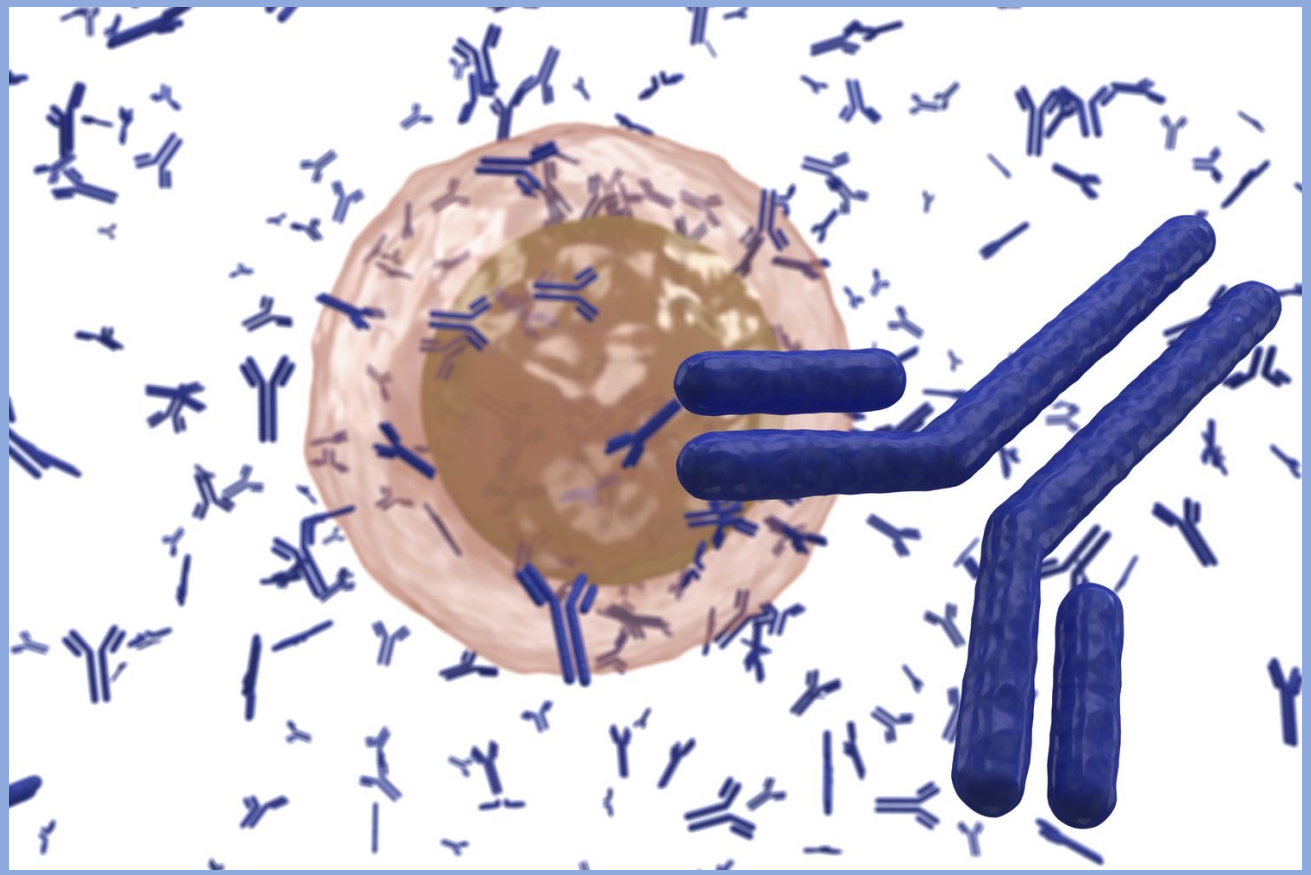
M Protein



M (myeloma or monoclonal) protein:

abnormal antibody or antibody fragment, such as an immunoglobulin light chain, that is produced in excess by an abnormal monoclonal proliferation of plasma cells, typically in multiple myeloma

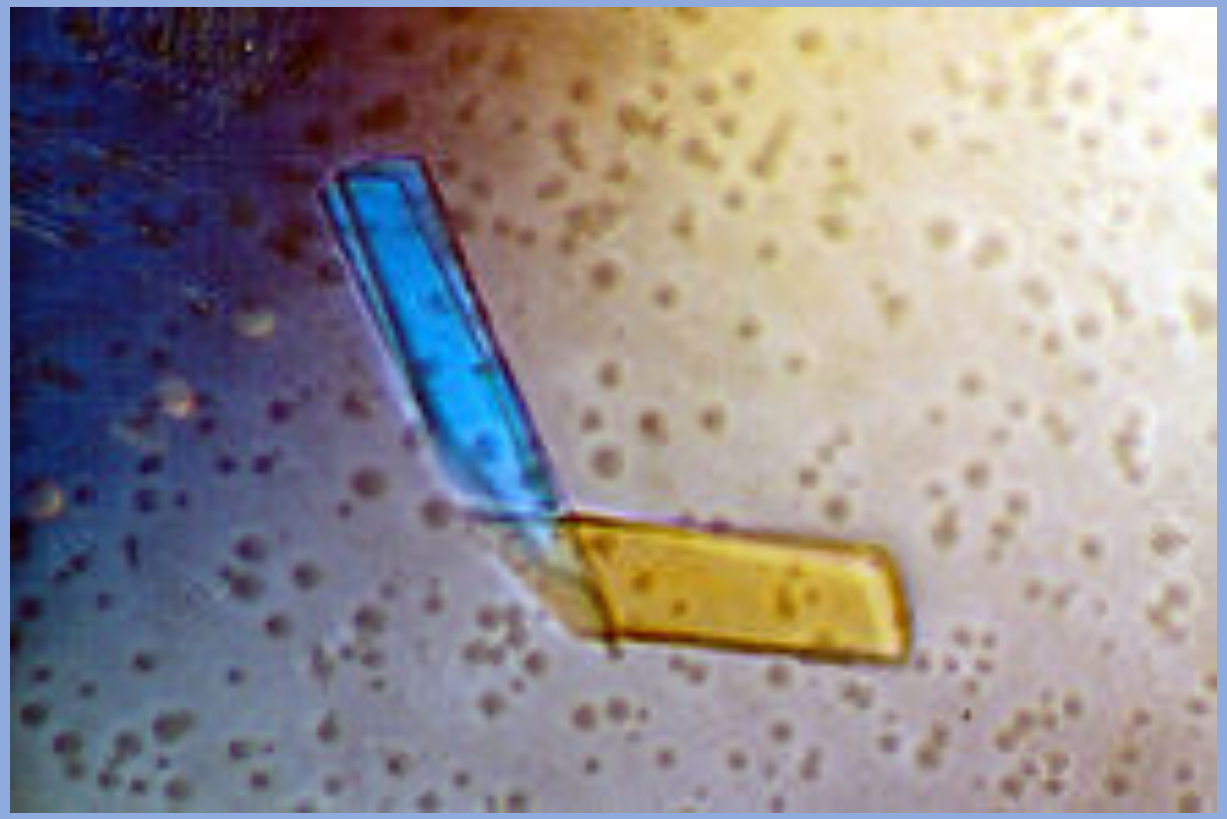
M Protein



Monoclonal gammopathy:

Accumulation of M-proteins in the blood, produced from a small number of atypical plasma cells

Bence-Jones Protein



Bence-Jones protein:

immunoglobulin light chains found in excessive quantities in urine in multiple myeloma

Etiology/Signalment

Solitary Extramedullary Cutaneous Plasmacytoma

- Extramedullary solitary plasmacytomas are *mostly cutaneous*
  - Also mouth, eye, GI tract, liver, brain, and SQ tissues

Etiology/Signalment

Solitary Extramedullary Cutaneous Plasmacytoma

- <u>Signalment:</u> Not established
- May be benign, but may also progress to systemic myeloma-related diseases

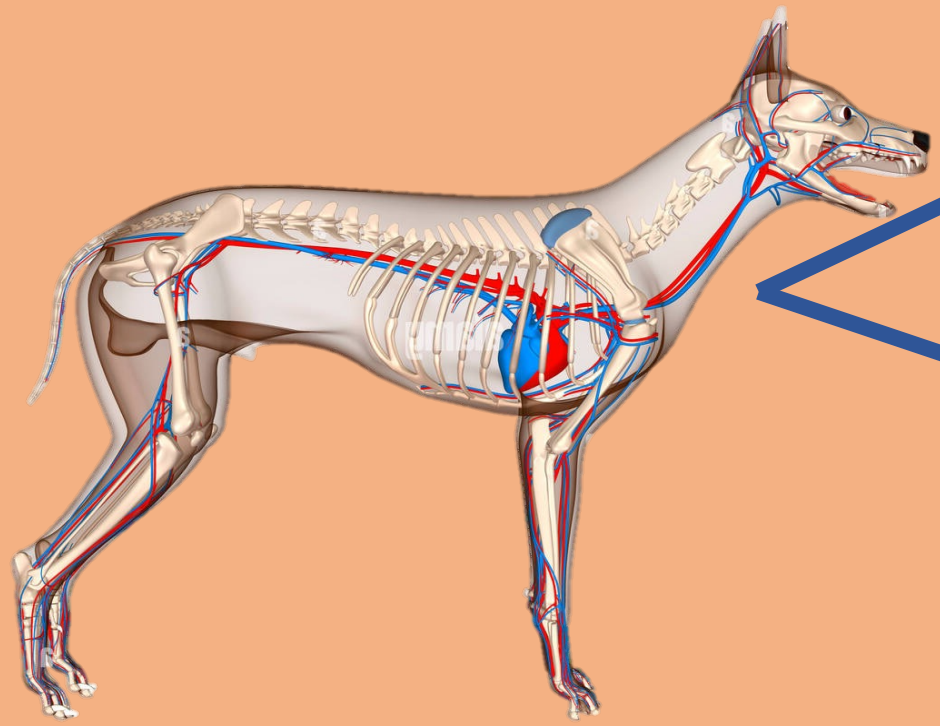
Treatment/Prognosis

Solitary Extramedullary Cutaneous Plasmacytoma

- **Treatment**: If confined to a local site and/or regional lymph nodes, sx excision and chemotherapy may result in long-term control
- **Prognosis**: Poorly defined (too rare). Early widespread metastasis and progression to multiple myeloma possible

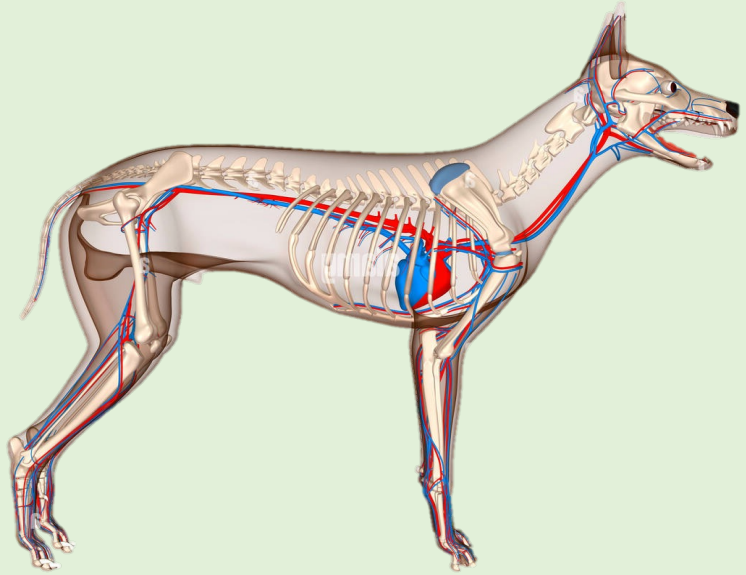
Cutaneous Plasmacytosis

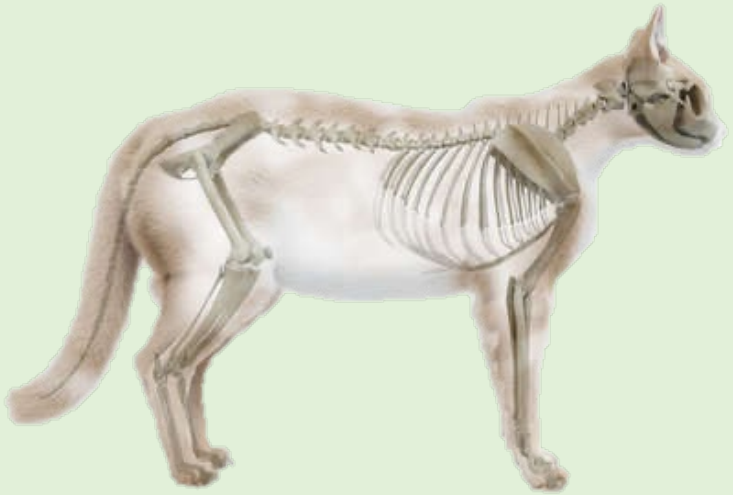
DOGS ONLY



- **Behavior:** Biologically aggressive
  - Lymph node or visceral involvement (30% cases)
  - +/- Monoclonal gammopathy
- **Signs:** 10s to 100s of cutaneous plasmacytomas
- **Treatment:** Systemic chemotherapy (melphalan = tx of choice).
- **Prognosis:** Similar to multiple myeloma

Cutaneous Metastasis from Multiple Myeloma



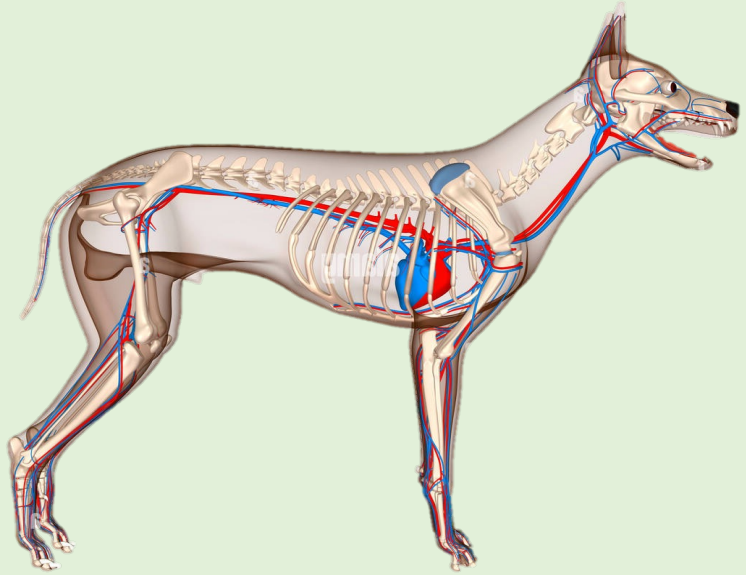


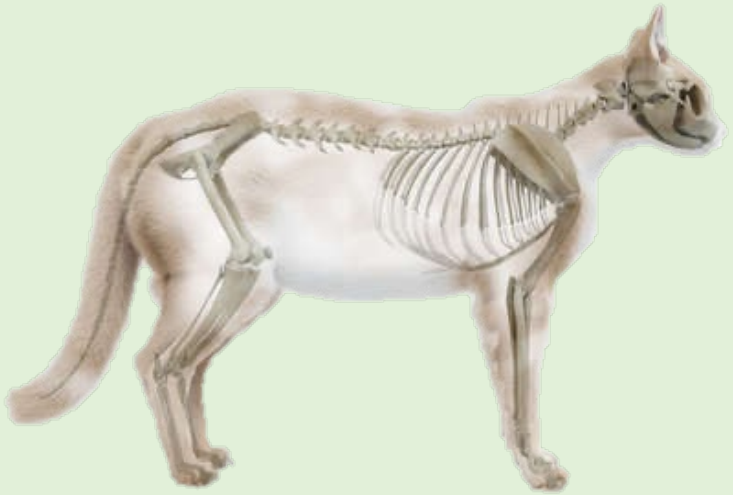
- <1% cutaneous plasma cell tumors are metastases from multiple myeloma

BUT

- Up to 30% cats with multiple myeloma will have cutaneous metastases

Cutaneous Metastasis from Multiple Myeloma





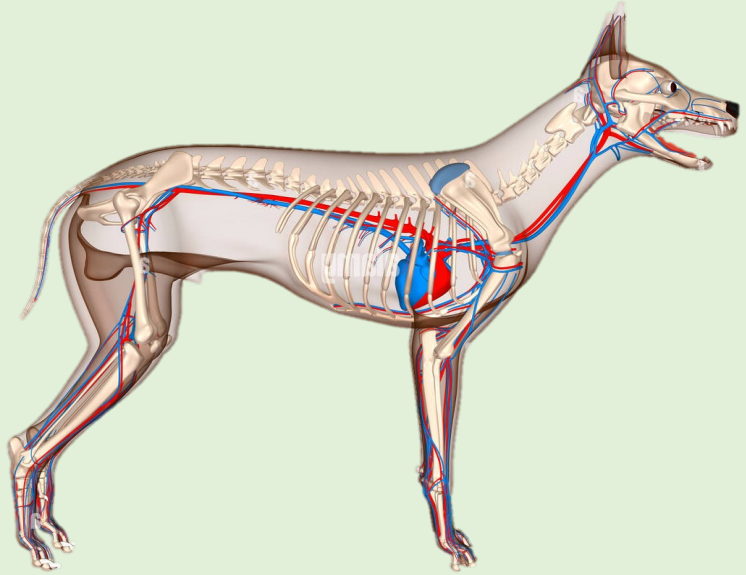
SYSTEMIC SIGNS

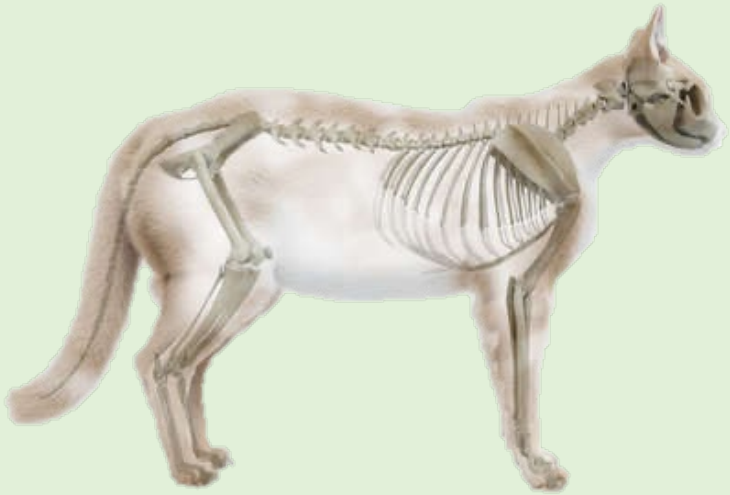
Associated with:

- **Infiltration with neoplastic plasma cells**
- **Circulating M-component**

- **Bone disease**
- **Bleeding diatheseis**
- **Hyperviscosity syndrome**
- **Cytopenia (myelophthisis)**
- **Heart failure**
- **Hypercalcemia**
- **Immunodeficiency / infections**
- **Renal disease**

Cutaneous Metastasis from Multiple Myeloma

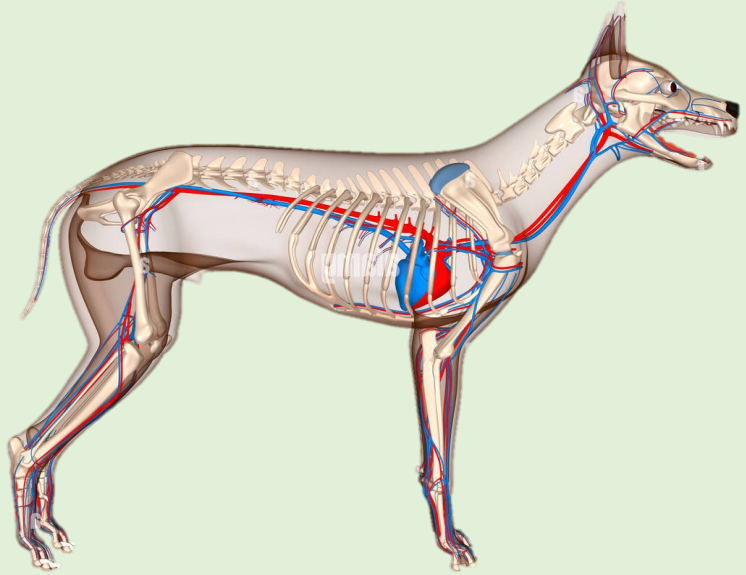


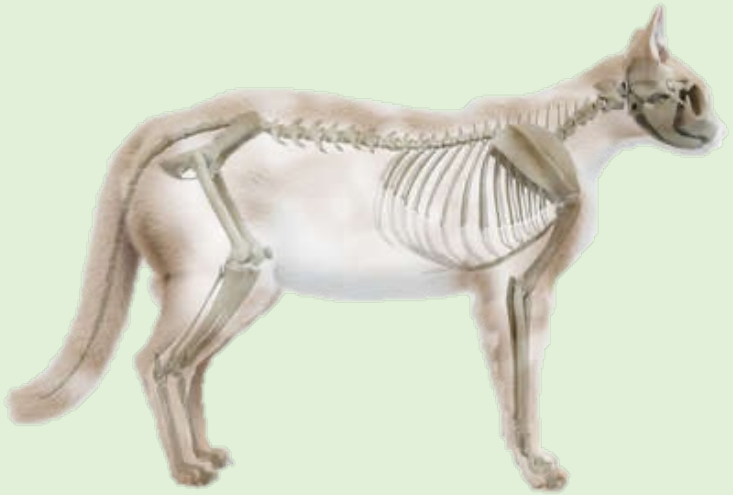


CUTANEOUS SIGNS

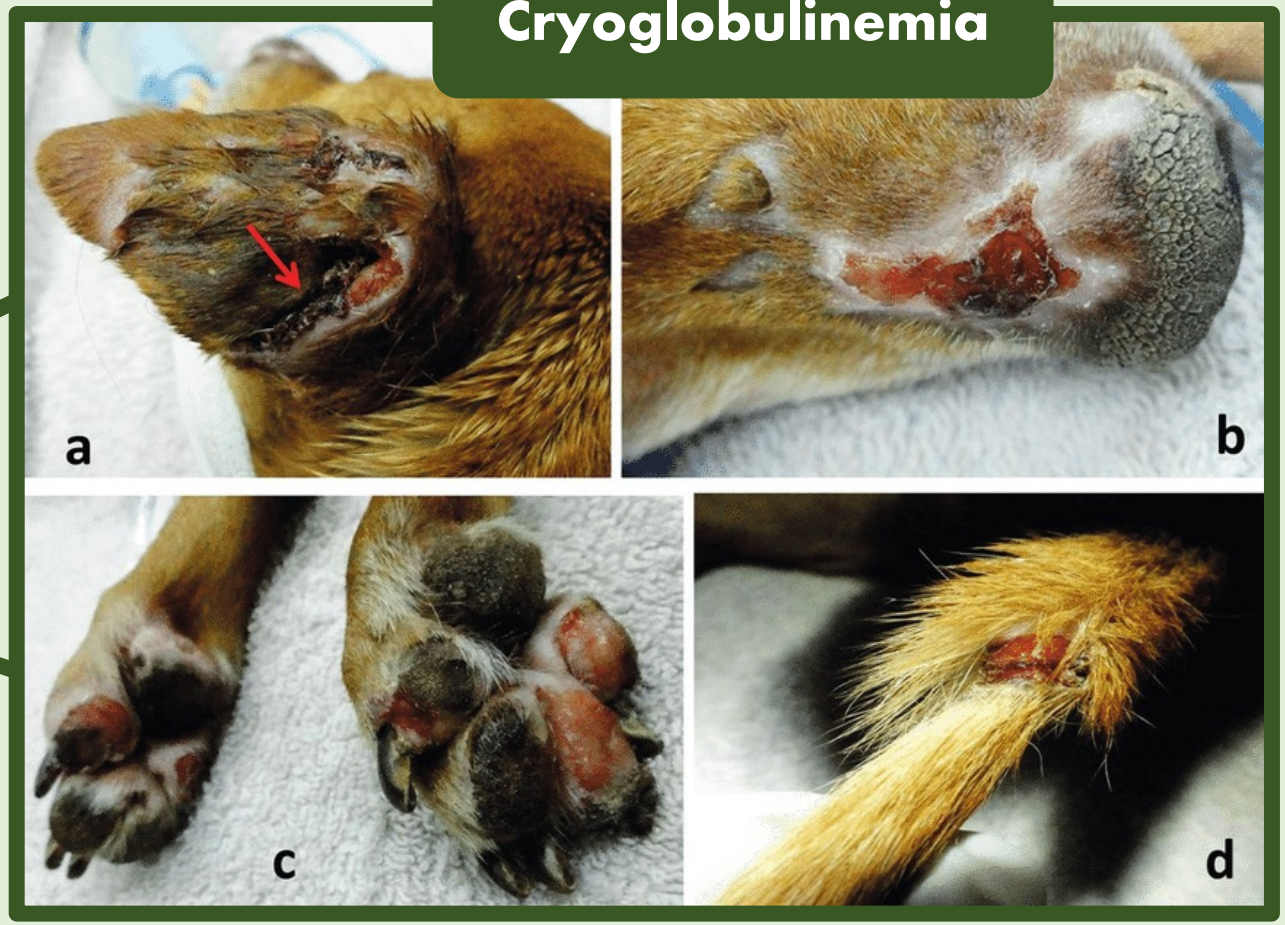
- Single or multiple nodules (dermal, SQ)
- Cryoglobulinemia / Cold Agglutinin Disease?

Cutaneous Metastasis from Multiple Myeloma





Cryoglobulinemia



Cutaneous Plasma Cell Disorders

Minimum Diagnostic Evaluation

Cytology

Labwork

Cutaneous Plasma Cell Disorders

Minimum Diagnostic Evaluation

Cytology

Numerous, well-differentiated plasma cells

Mott cells (Russell bodies)

Cutaneous Plasma Cell Disorders

Minimum Diagnostic Evaluation

Labwork

CBC, chem, UA, ionized calcium

Pay attention to RENAL FUNCTION and SERUM CALCIUM

Cutaneous Plasma Cell Disorders

Additional Testing Options

Histopathology

IHC

PARR testing

Staging

Cutaneous Plasma Cell Disorders

IHC

PARR testing

Additional Testing Options

Used to differentiate from other round cell tumors

- **IHC**
  - **MM-1/interferon regulatory factor-4 (MUM1/IRF4)**
  - **Immunoglobulin light and heavy chains**
  - **Thioflavin T**

Cutaneous Plasma Cell Disorders

Additional Testing Options

Staging

- Cutaneous plasmacytosis and multiple myeloma – important, high metastatic rate
- Cutaneous solitary extramedullary plasmacytomas – less important
- Tests:
  - Bone marrow aspirate
  - Bone imaging
  - Systemic imaging
  - Demonstration of serum or urine M component