

Canine Lymphoma

Logistics of Diagnosis and Treatment

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SMALL ANIMAL ONCOLOGY



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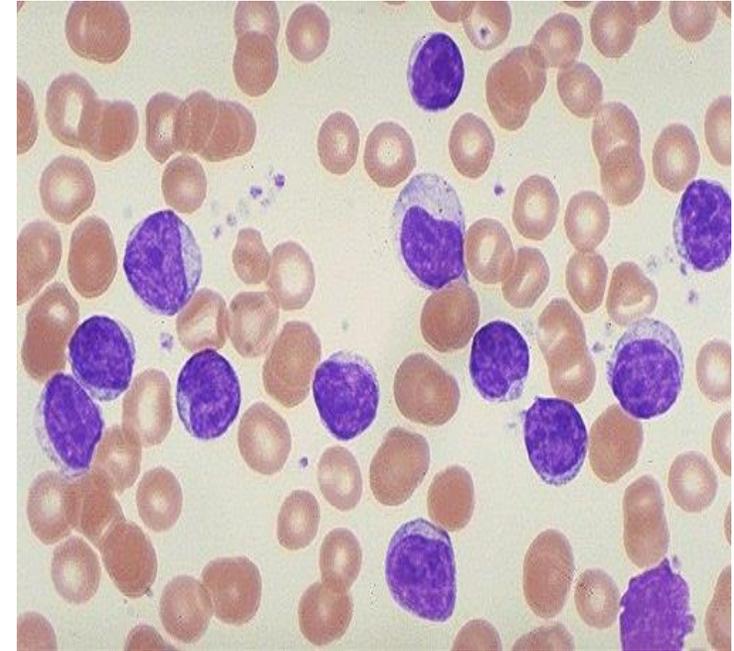
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What is Lymphoma?

- * Cancer of lymphocytes
- * Arises from lymphoid tissues
 - Lymph nodes
 - Spleen
 - Liver
 - Bone Marrow
 - Blood



- * One of the most common neoplasms in dogs

Common Signalments

* Middle aged to older dogs
(6-9 years of age)

* T-cell lymphoma = usually
younger dogs

* Which breeds are
predisposed?



Causes of Lymphoma

- * Largely unknown
- * Likely a combination of different factors
 - Genetic predisposition
 - Exposure to chemicals and/or radiation
 - Viral or bacterial exposure
- * Ongoing research to investigate possible causes and correlations
 - Genetic and molecular factors
 - Infectious factors
 - Environmental factors
 - Immunologic factors



Classifying Lymphoma

- * Anatomic location

- Multicentric/generalized nodal = 83%
- GI = 6%
- Cutaneous = 5%
- Mediastinal = 2%
- Extranodal = 2%

- * Histologic criteria

- * Immunophenotypic characteristics



Stages of Lymphoma

Stage I

- Single lymph node enlargement (rare)

Stage II

- Regional lymph node enlargement

Stage III

- Generalized lymph node enlargement

Stage IV

- Generalized lymph node enlargement with liver and/or spleen involvement

Stage V

- Bone marrow and/or blood involvement, other organ involvement



Substages of Lymphoma

Substage a

- No signs of clinical signs of illness



Substage b

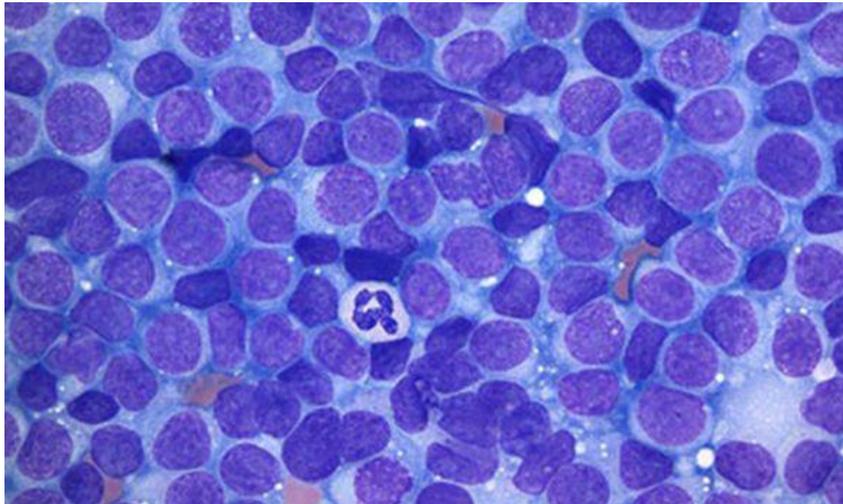
- Showing signs of illness



Grades of Lymphoma

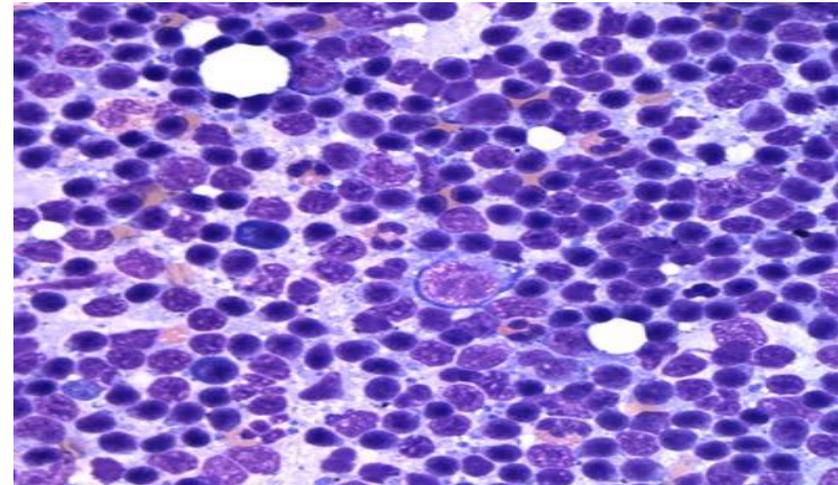
**High/intermediate grade =
large/intermediate cell =
lymphoblastic**

- Typically biologically aggressive and rapidly progressive
- Requires aggressive, more intense therapy



Low grade = small cell = indolent

- Typically biologically indolent and slowly progressive
- May not require any therapy (monitoring)
- Therapy typically differs (less intense) than for high grade



Types of Lymphoma

B-Cell Lymphoma

- 2/3 of k-9 lymphoma cases
- Better response and prognosis
- Mean survival time ~ 12 months (with CHOP chemotherapy)

T-Cell Lymphoma

- 1/3 of k-9 lymphoma cases
- Worse prognosis and lower chemotherapy response rate
 - More likely to have hypercalcemia
 - Mean survival time ~ 6-8 months (with CHOP chemotherapy)
 - Sites: skin, mediastinum, GI, hepatic



Immunophenotyping (B vs. T cell)

FLOW CYTOMETRY

Performed on:

- Blood
- Bone marrow
- Lymph node
- Effusion
- Mediastinal mass

Panel of antibodies

- Phenotype, subtype, MHC II, etc

Overnight shipping

NC St/CSU

Turn around ~3-5 days

PARR

Performed on:

- Blood
- Bone marrow
- Lymph node
 - Stained slides***
- Effusion
- Mediastinal mass

Clonality to distinguish reactive lymphocytosis vs. leukemia

NC St/CSU/Davis/MSU

Turn around ~ 3-10 days

***Stained cytology or formalin-fixed pathology samples



Prognostic Factors

Stage of disease

- Stage V = worse prognosis

Substage a > b

- Most consistent prognostic indicator

Immunophenotype

- B cell > T cell

Anatomic form:

- Mediastinal (Poor)
- Gastrointestinal (Poor)
- Hepatic (Poor)
- Cutaneous (Poor)

Prior prednisone

- Increased drug resistance if > 2 weeks

Histologic grade:

- Low grade = better prognosis

Hypercalcemia

- Mediastinal form/T cell (Poor)

Anemia

- Poorer prognosis (<30%)

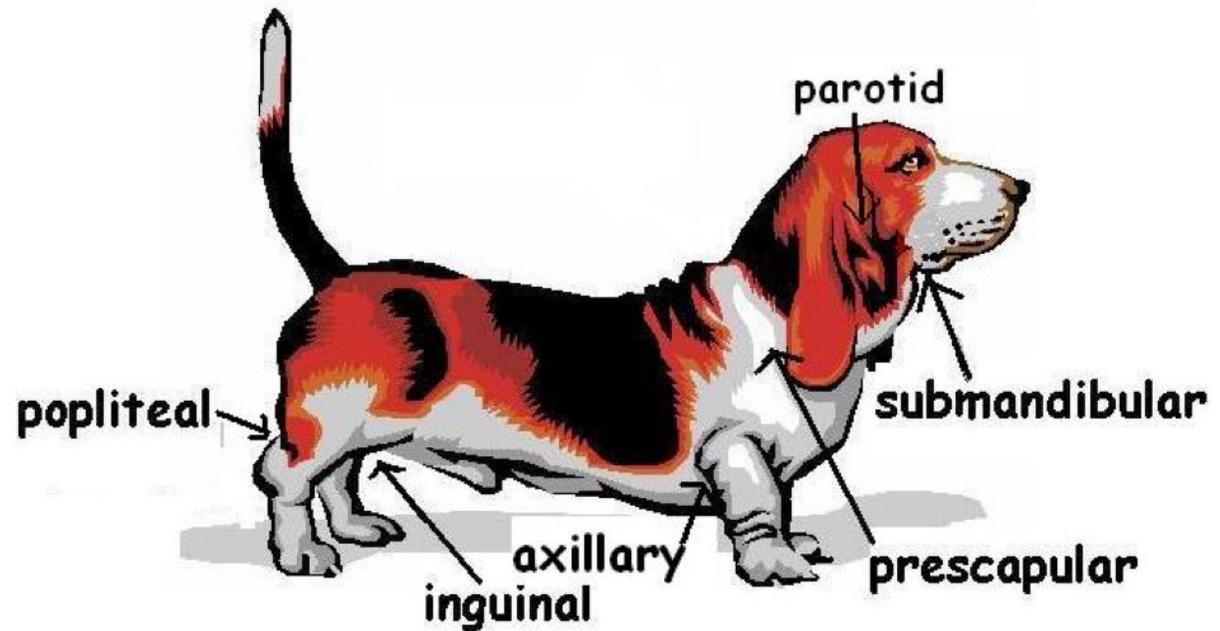
Chemotherapy induced hematologic toxicity

- Longer survival

Clinical Signs

Variable based on tumor location

- Generalized lymphadenopathy (multicentric = most common)
- Inappetence
- Weight loss
- Vomiting/diarrhea
- Dyspnea
- Fever
- PU/PD: hypercalcemia
 - ~15% of cases
 - 40% in mediastinal



Diagnosing Lymphoma: Cytology

Lymph node aspirates

- Sample at least TWO nodes
- Prescapular and popliteal lymph nodes if multiple are enlarged

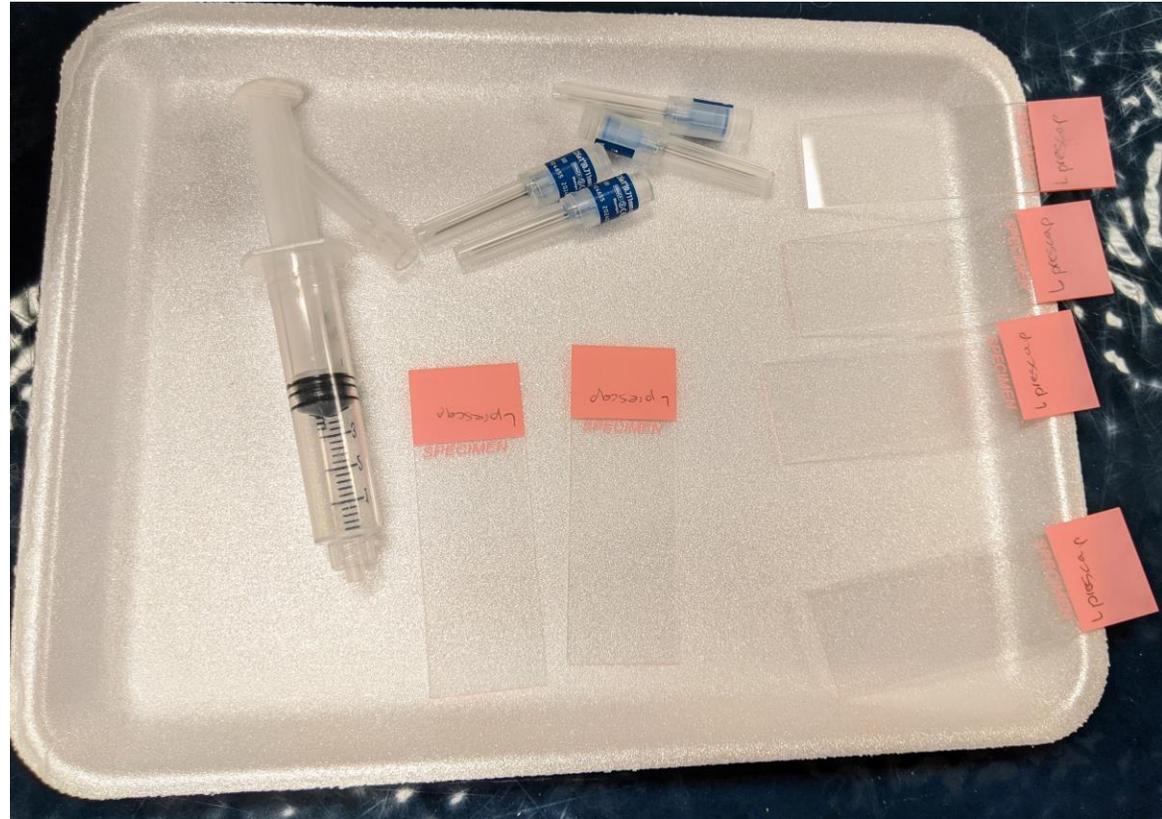


Diagnosing Lymphoma: Lymph Node Aspirates

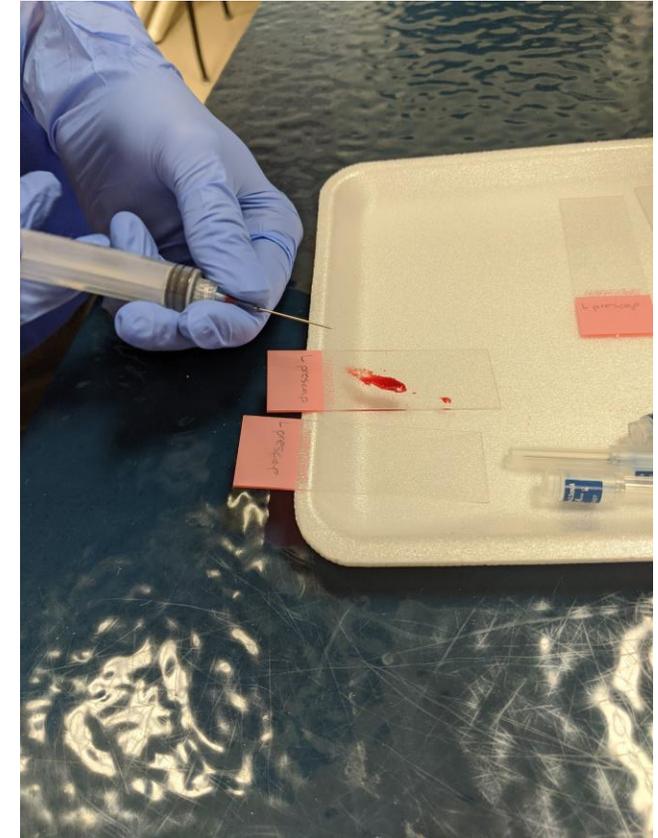
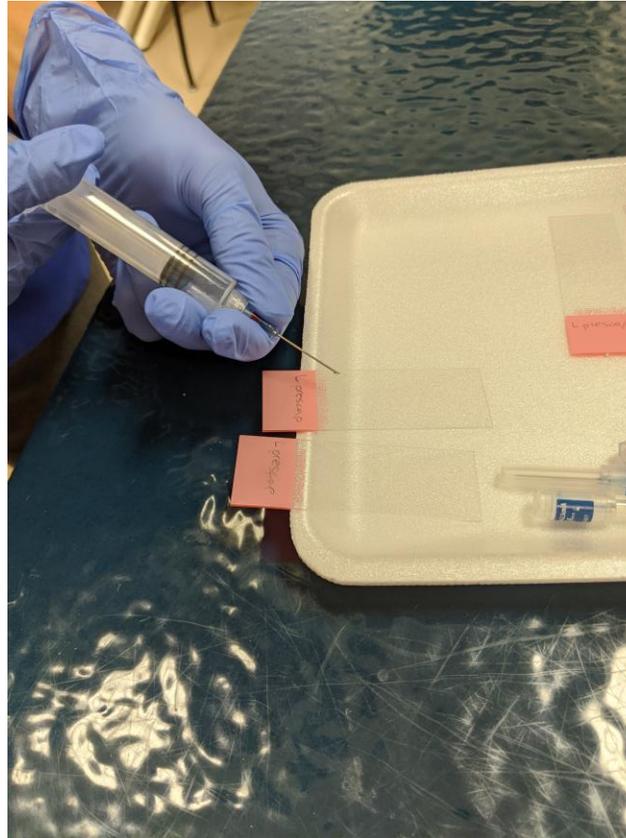


Diagnosing Lymphoma: Lymph Node Aspirate Supplies

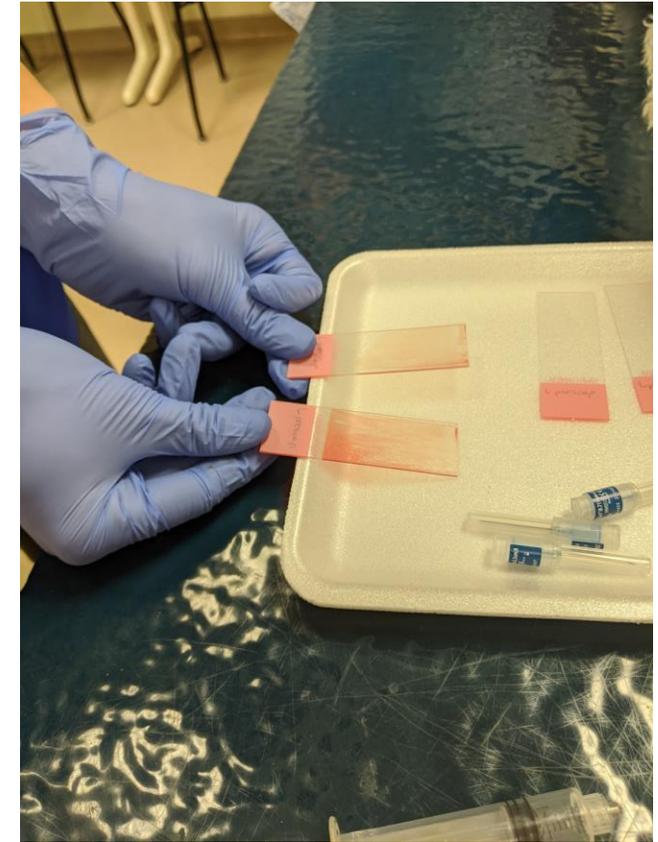
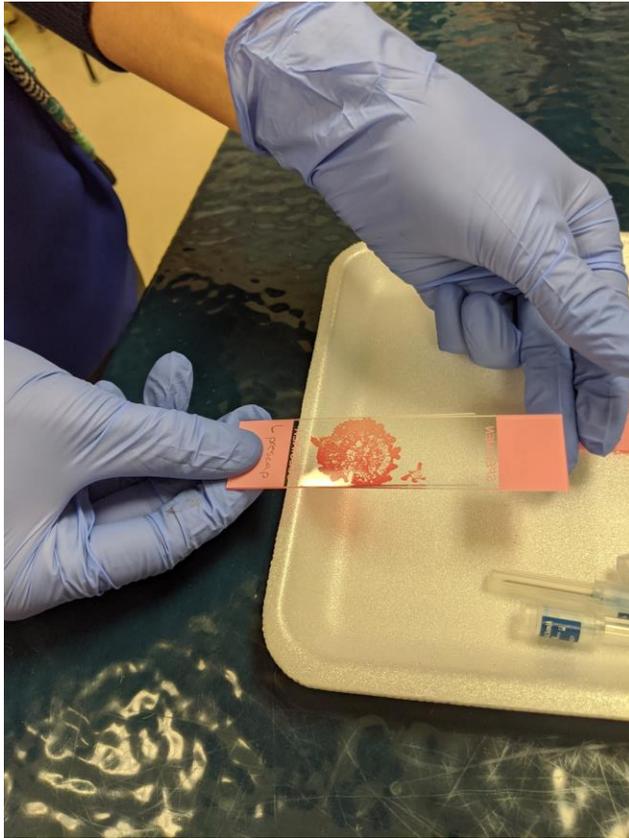
- Preferred method:
 - Fenestration (no syringe attached)
- Supplies needed
 - 6ml syringe
 - 22 gauge needles
 - Microscope slides



Diagnosing Lymphoma: Lymph Node Aspirates



Diagnosing Lymphoma: Lymph Node Aspirates



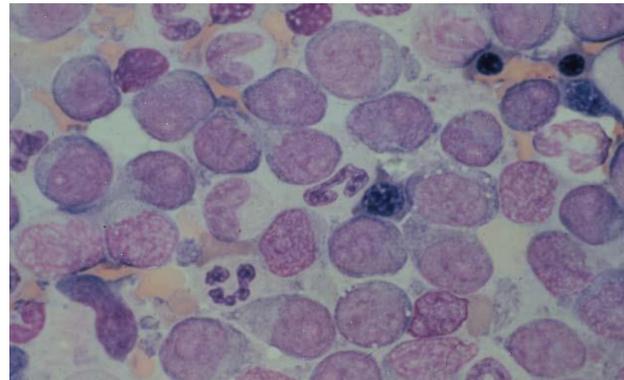
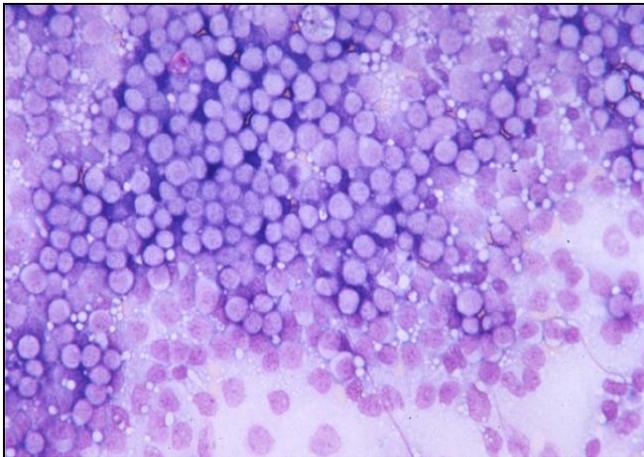
Diagnosing Lymphoma: Cytology

Usually adequate for diagnosis

- 80-90% via cytology
- Lymph node or internal organ aspirate

Immunophenotyping

- Immunocytochemistry (ICC)



Non-pathologist diagnosis of lymphoma

- Cells are larger than a neutrophil
- Absence of plasma cells
- Variability in nucleolar size/number

Diagnosing Lymphoma: Lymph Node Removal or Punch Biopsy

Consider when cytology is inconclusive

Lymph node removal is preferred over biopsy

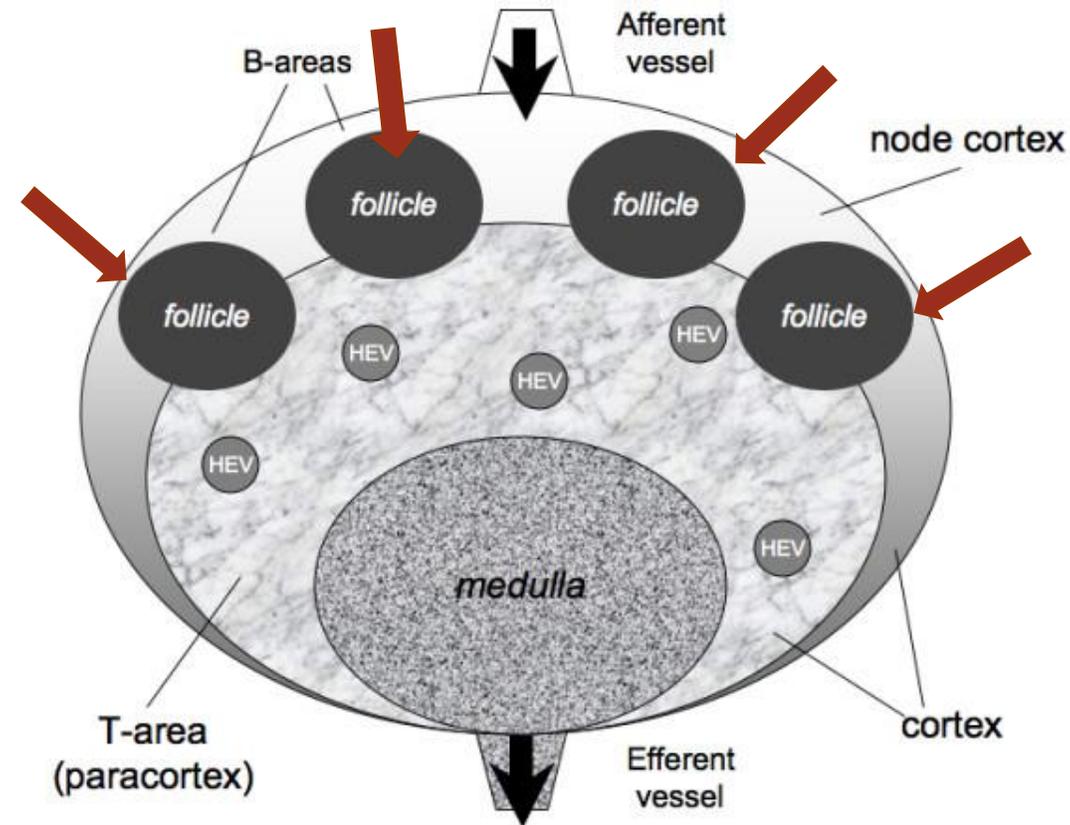
- More invasive
- Requires anesthesia or heavy sedation
- Pain medications

Potential Complications

- Incision site infection
- Accidental removal of salivary glands (mandibular L.N. removal)
- Lymphedema



Anatomy of a Lymph Node



Staging Considerations

Physical exam

Minimum data base (CBC, Chem, UA)

- **CBC**

- Anemia
- Thrombocytopenia
- Leukopenia
- Blasts (stage V)

- **Chemistry Panel**

- Hypercalcemia
- Hepatic involvement (ALT)



Staging Considerations Continued

Thoracic radiographs 3-view

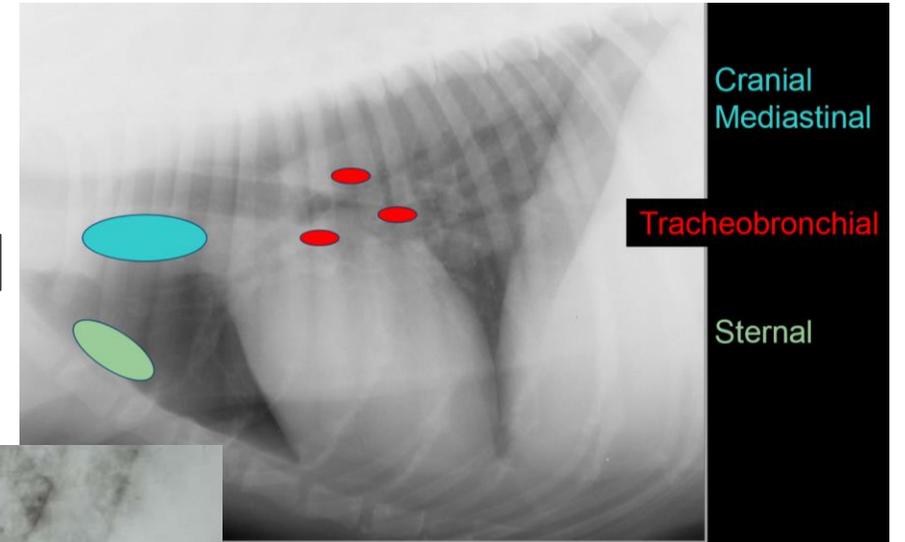
- Mediastinal mass, pulmonary lesions, lymph nodes

Abdominal radiographs and/or ultrasound

- LNs, hepatic, splenic involvement, GI tract

Bone marrow aspirate

- Determine if stage V
- Rarely needed for diagnosis



Treatment Options

Treatment	B Cell Survival Time	T Cell Survival Time
(L)CHOP (multi-agent) chemotherapy	12 months; 25% live to 2 years	6-8 months
Tanovea +Doxorubicin	12 months	6-8 months
Tanovea (single agent)	4-5 months	2 weeks
Doxorubicin (single-agent)	5-7 months	4-5 months
Lomustine/CCNU (single-agent)	3-4 months	2-3 months
Prednisone	4-8 weeks	4-8 weeks

**IMPORTANT: These numbers are averages...
some dogs do better, some worse.**



Treatment Options: (L)CHOP (Multi-agent)

L-Asparaginase, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

- 15 week to 6 month protocol
- IV and oral medications

Response Rate:

- 80-95%
- Duration of response: 6-9 months

Survival:

- 12 months (median)
- 10-25% 2-year survival

Considerations

- Scheduling
 - Treated weekly for 16 weeks



Cost estimate: \$5,000-\$6,000

Treatment Options: Tanovea + Doxorubicin

Tanovea + DOX

- IV administration
- Alternating every 3 weeks
- 3 doses each (6 total treatments)

Response rate:

- 84% (PFI = 6 months)
 - 68% clinical remission
 - 16% partial remission

Survival:

- Similar to CHOP
 - 12 months (median)

Considerations:

- Drug availability
- Fewer clinic visits
- Results similar to CHOP



Cost estimate: \$5,000-\$6,000

Treatment Options: Tanovea

Tanovea:

- Every 3 weeks x 5 doses
- IV administration (30 minute infusion)
- Severe vesicant

Response rate:

- 79%

Remission duration:

- 4-5 months

Considerations:

- Drug availability
- Fewer clinic visits
- 4% develop pulmonary fibrosis



**Cost estimate: \$6,000-\$8,000
depending on size of patient**

Treatment Options: Doxorubicin

Doxorubicin

- Every 3 weeks x 3-5 treatments
- IV Administration (10 minute infusion)
- Severe vesicant

Response rate:

- 60-80%

Survival:

- 5-7 months (median)

Considerations:

- Fewer clinic visits
- Cardiac considerations



Cost Estimate: \$400-\$600 per treatment
\$600 x 5 treatments = \$3,000

Treatment Options: CCNU (Lomustine)

CCNU

- Administered orally
- Dosed monthly (Q3 weeks)
- Given until intolerance or disease progression

Response rate:

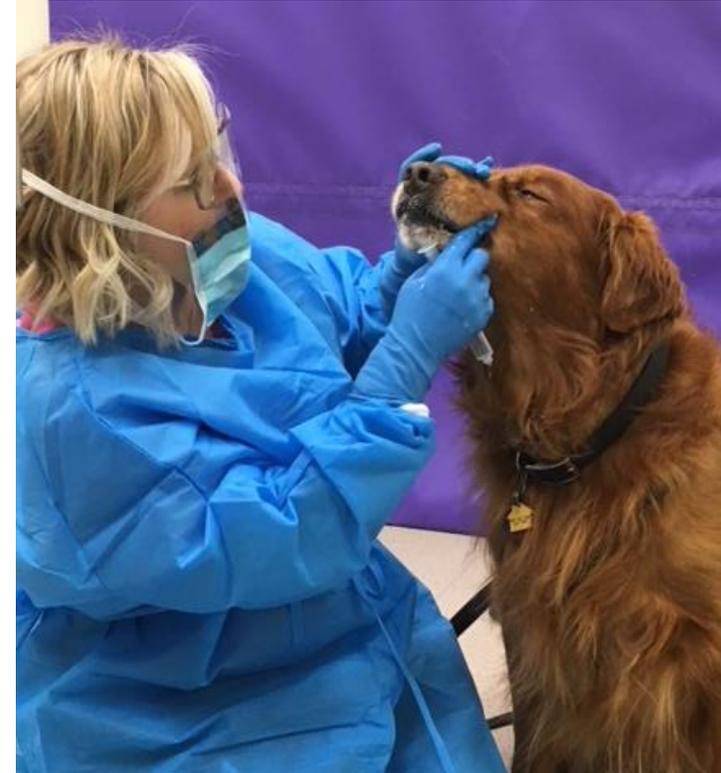
- 40-50%

Survival:

- 2-4 months (median)

Considerations:

- Oral medication
- Ease of scheduling



Cost estimate: \$250 per treatment

Treatment Options: Prednisone Alone

Palliative option

- 40mg/M² PO SID (one week)
- 20 mg/M² PO SID (indefinitely)

No turning back?

- Prior Prednisone = poor prognosis
- Possible multi-drug resistance

Response rate:

- 50%

Survival:

- 1-2 months (median)



Do not administer Prednisone until you have your diagnosis!

Treatment Considerations

Treatment Goals

- Objective: Complete Remission (CR)
 - CR rate and duration varies based on protocol used
- Subjective: Quality of Life

Assessing remission

- Physical Exam/lymph node palpation
- Cytology

**Obtaining CR = main goal of treatment
Balancing with a good QOL**



Treatment Considerations : MDR1 Gene Mutation

What is it?

- Genetic Mutation
- Responsible for production of P-glycoprotein
 - Transports drugs out of brain
- Mutation inhibits ability to remove certain drugs from brain
 - Build up of toxins
 - Severe adverse reactions

Who is affected?

- Herding breeds and some sighthounds
- Complete list found via Washington State website
 - <https://vcpl.vetmed.wsu.edu/affected-breeds>



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Treatment Considerations : MDR1 Gene Mutation

Drug Sensitivities

Acepromazine	Milbemycin
Butorphanol	Moxidectin
Doramectin	Paclitaxel
Doxorubicin	Selamectin
Erythromycin	Vinblastine
Ivermectin	Vincristine
Loperamide	Vinorelbine

How to Test

2 ML whole blood in EDTA tube
OR
Cheek swab sample
Send to Washington State University



Treatment Considerations : MDR1 Gene Mutation

Normal/Normal

- No mutation
- **Will not** pass to offspring
- Should tolerate normal drug dosing



Normal/Mutant

- Carry mutation
- **MAY** pass to offspring
- **MAY** experience drug toxicity with normal dosing
- Dose reduce by 25% for chemotherapy

WSU Veterinary Clinical
Pharmacology Lab
Phone: 509-335-3745
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Email: VCPL@vetmed.wsu.edu

Mutant/Mutant

- Carry mutation
- **WILL** pass to offspring
- **WILL** experience drug toxicity with normal dosing
- Dose reduce by 50% for chemotherapy **OR** consider non-MDR drugs

Treatment Considerations: Side Effects

Bone Marrow Suppression

- **Neutropenia**
 - More prone to infection
 - May need antibiotics if Neutrophil count falls below threshold
 - Usually above 2,000
- **Thrombocytopenia**
 - More prone to bruising or bleeding
 - Usually above 60,000
- **Loss of Red Blood Cells**
 - Increased tiredness or difficulty breathing
- CBC is performed before each treatment



Treatment Considerations: Side Effects

Gastrointestinal

- **Vomiting**

- Is it due to nausea?
 - Maropitant (Cerenia)
 - 2mg/kg PO SID

- **Inappetence**

- Is it due to nausea?
 - Entyce (Capromorelin)
 - 3mg/kg (1ml/10lb) PO SID @ least 4 days

- **Diarrhea**

- Metronidazole
 - 10-15mg/kg PO Q12H for two days post resolution of symptoms
 - Not to exceed 15mg/kg



Treatment Considerations: Side Effects

Skin Pigmentation

- Can darken with chemotherapy

Hair Loss

- Uncommon
- May change in texture or color



Treatment Considerations: Side Effects

Extravasation of Chemotherapy



Doxorubicin



Tanovea



Vincristine

Treatment Considerations: Safety

Clinic Safety

- Who could be exposed??
- Facility and engineering controls
 - USP 800 compliant
- Proper waste segregation and disposal
- PPE for all personnel handling hazardous drugs and drug waste
 - Chemo rated gowns (impermeable)
 - Chemo rated gloves (two pairs per person)
 - Goggles
- Spill kit availability
- Closed system transfer device
 - Is illegal to administer chemo without!



Treatment Considerations: Safety

Client Safety and Education

- Chemotherapy metabolites in bodily fluids
 - Avoid contact with stool, urine, vomit & saliva for 72 hours post treatment
 - Walk pets in a low traffic area
- Soiled laundry/bedding
 - Wash twice in hot water, separate from other laundry
- Messes indoors
 - Never spray mess with cleaner!
 - Aerosolizes metabolites
 - Always wear gloves
- Who could be exposed??
 - Pregnant/nursing
 - Trying to conceive?
 - Immunocompromised
 - Children



Lymphoma: Take Home Points

Peripheral Lymphadenopathy

- Importance of early diagnosis- aspirate!

Diagnosing

- Lymph node cytology
 - Sample at least 2 nodes (prescapular and popliteal ideal)
 - Evaluate sample quality in-house, send out for pathologist confirmation
- Lymph node biopsy
 - Whole node is preferred over punch biopsy

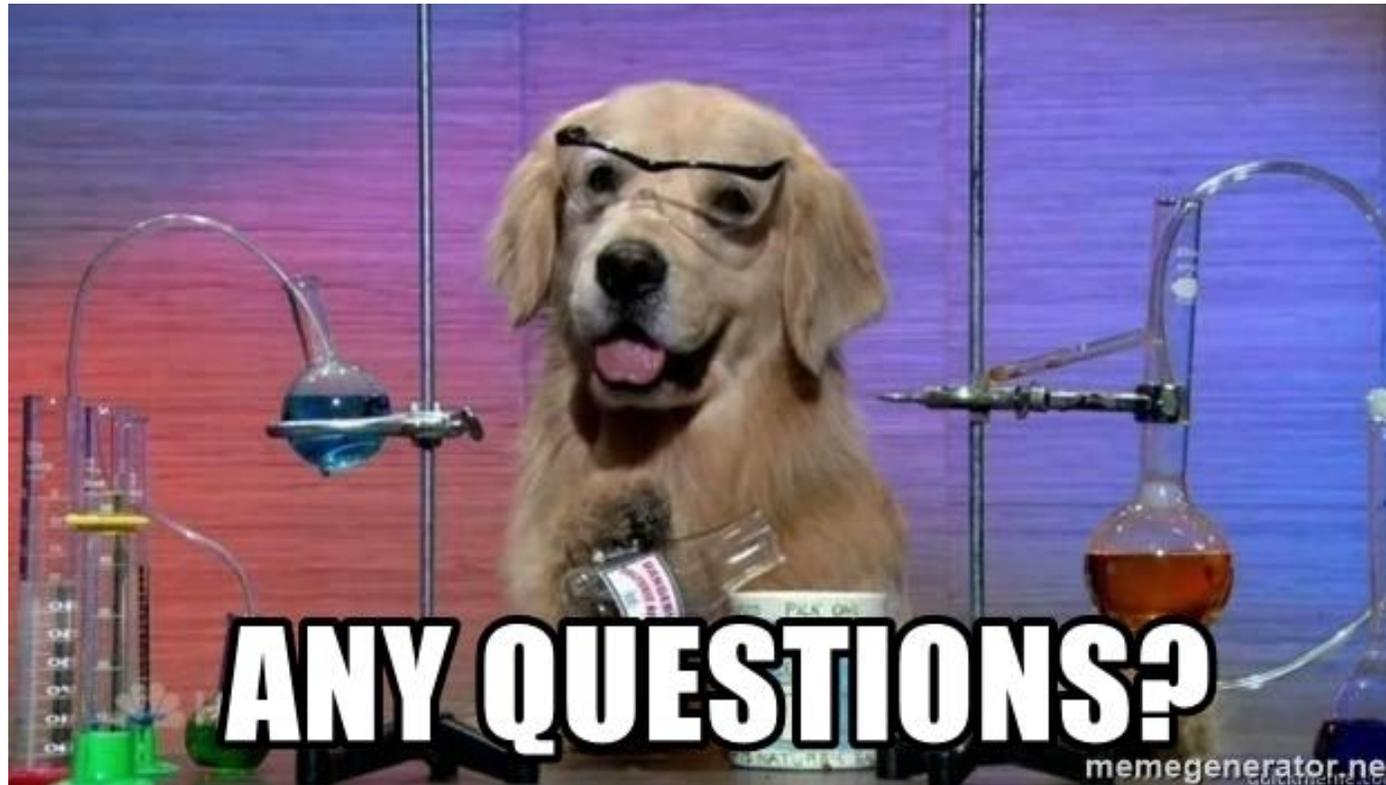
Treatment with Prednisone

- Do not start Prednisone before chemotherapy or before getting a diagnosis!
 - May cause resistance to chemo if given for extended time prior to tx
 - May make diagnosing more difficult or sometimes not possible

MDR1 gene mutation

- Consider prophylactically testing all at-risk breeds
- **ALWAYS** test at-risk breeds **BEFORE** administering drugs on sensitivity list





Email: oncotech@iastate.edu

Website: <https://www.vetmed.iastate.edu/vmc/small-animal/specialty-care/oncology>

