

Canine multicentric lymphoma, like it or lump it



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Disclosure

- I am an IDEXX employee
- Legal disclaimer: The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation, and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions, and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.

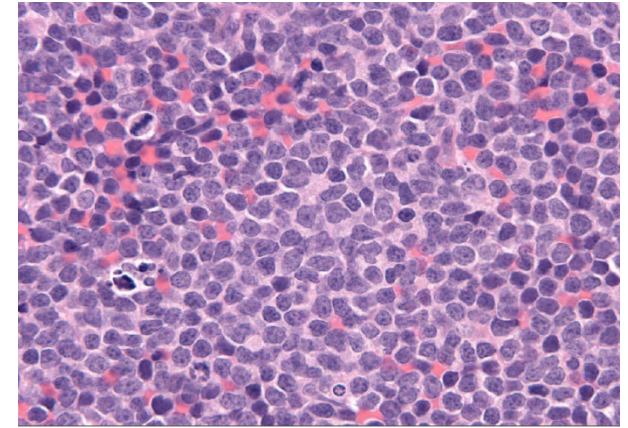
Outline: Canine Lymphoma (LSA)

- Epidemiology
- Clinical presentations
- Classification / Biological behaviour /Prognosis
- Diagnostic tests
 - Cytology and ancillary tests
 - Histopathology and immunophenotyping
- Treatment and prognosis



Epidemiology

- Most common canine haematopoietic neoplasia
- Breed predisposition: Boxer, Golden Retriever, Rottweiler, WHWT
- Genetic predisposition
- Lymphohematopoietic organs >>extranodal
- Most common presentation is **multicentric** with peripheral lymphadenopathy
 - +/- spleen/liver/ bone marrow involvement
- As a systemic disease it is treated with chemotherapy
- Other presentations: GI, cutaneous, nasal, ocular, CNS, renal - differ in prognosis

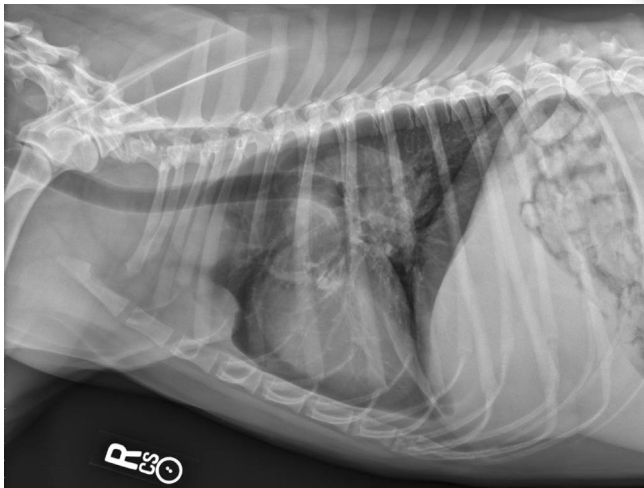


(Credits: IDEXX)

(Vail et al. 2020)



Lymphoma

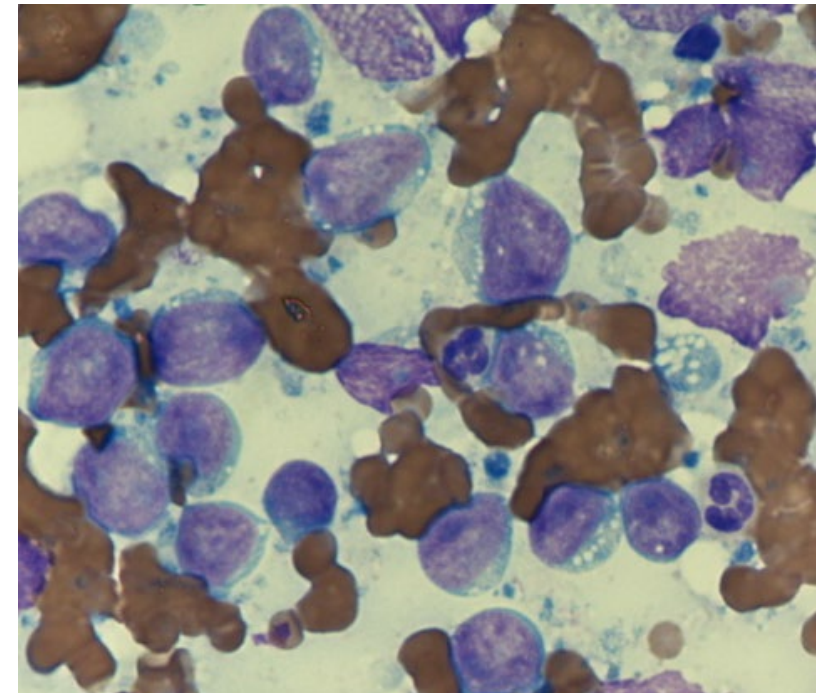
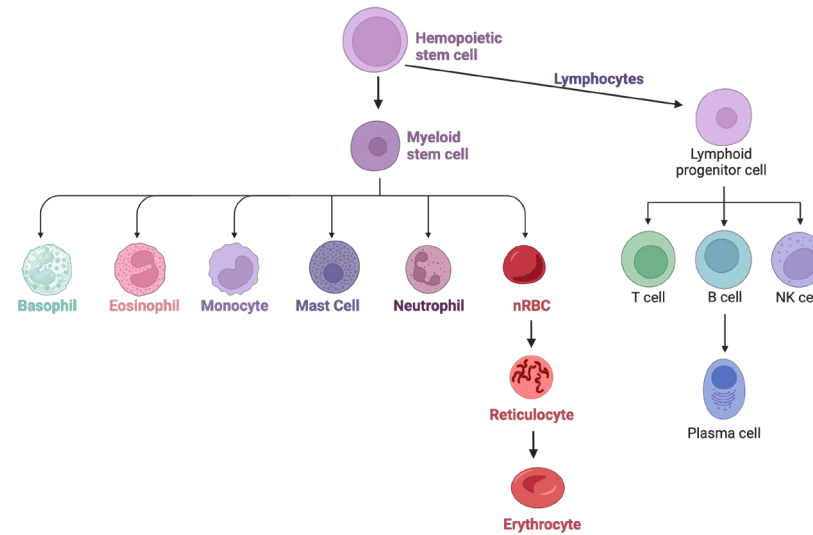




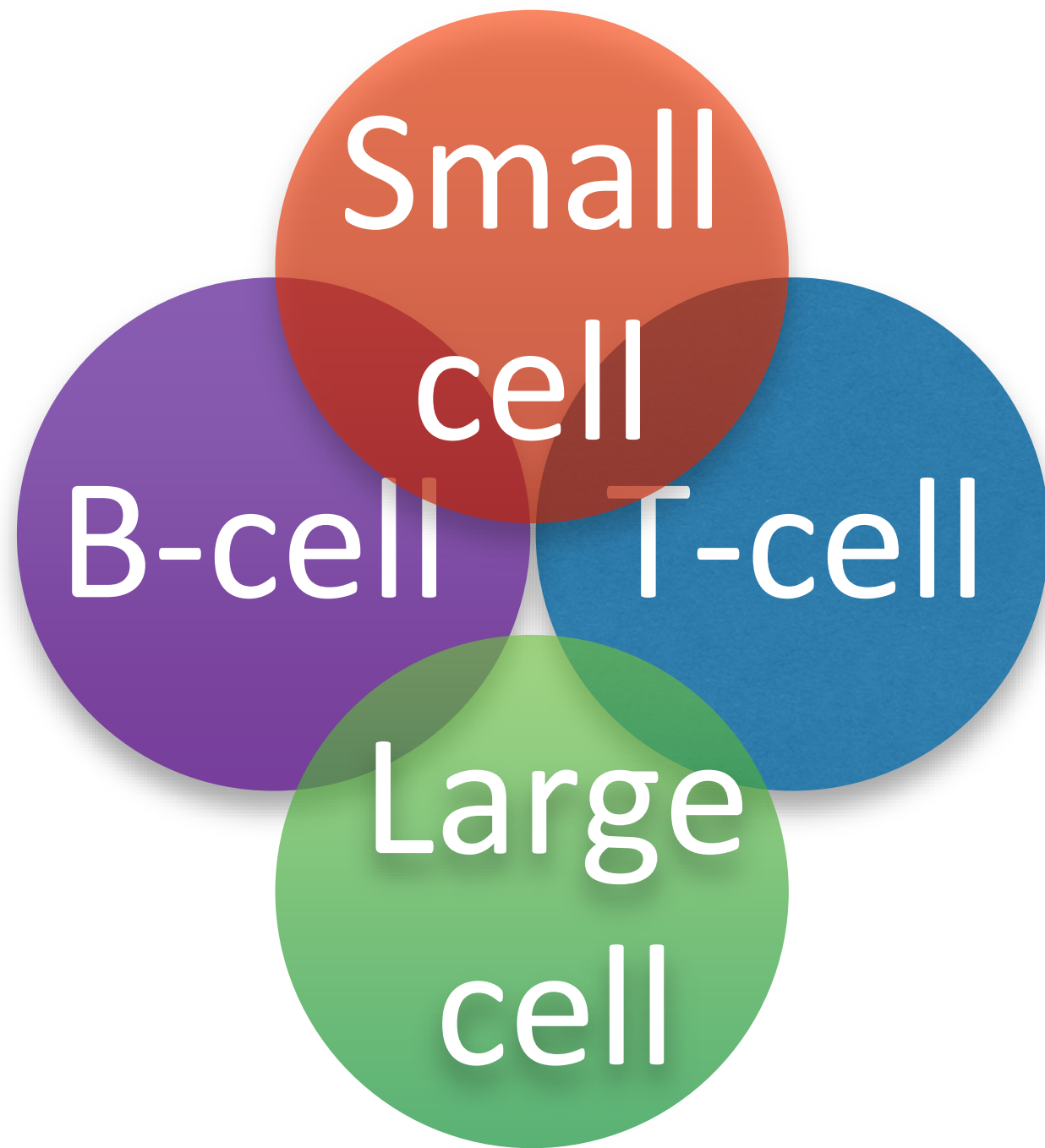
(Pictures courtesy of Dr. G.C. Couto)

Variable biological behavior WHY?

- Different lymphocyte **phenotypes** (B, T, NK)
- Clonal proliferation at **any** stage of maturation
- Malignant transformation multifactorial: chromosomal aberrations, breed predisposition, environmental, immunologic...



(Picture: A Lara Garcia)



Small
cell

B-cell

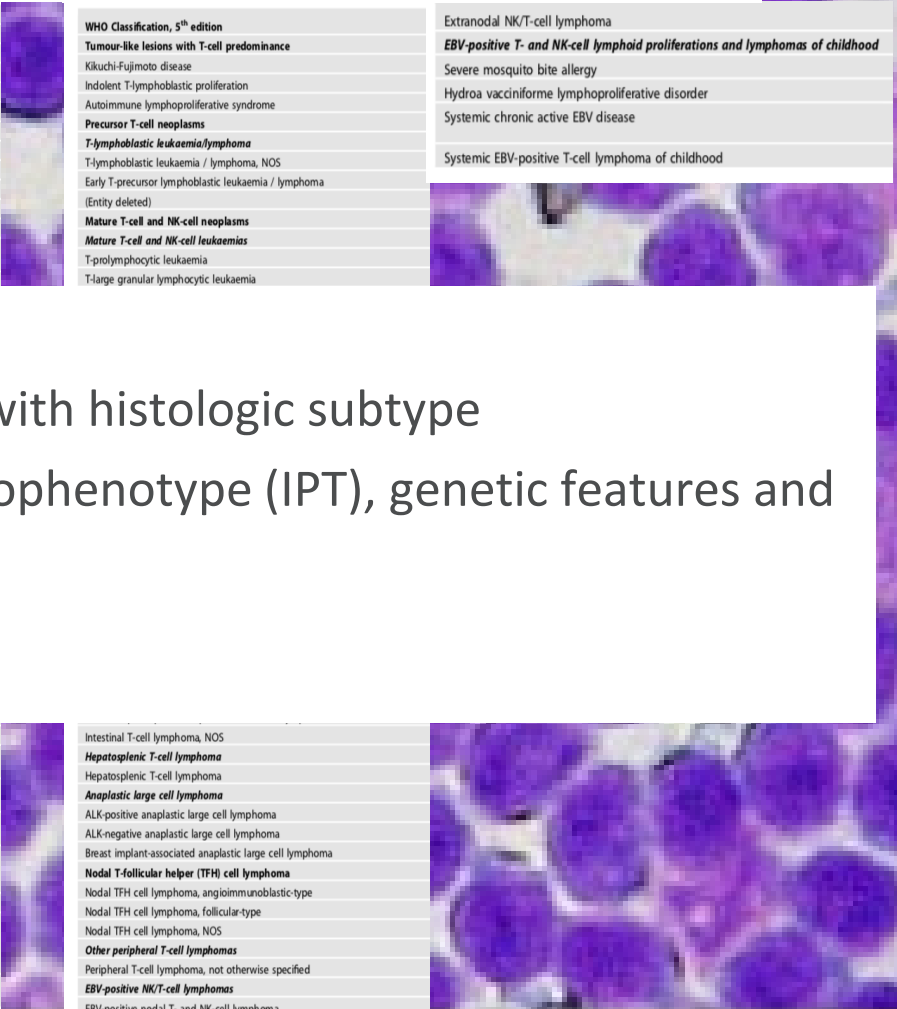
T-cell

Large
cell

Morphologic classification of lymphoma and prognosis

WHO Classification applied to K9 LSA

5TH EDITION WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF LYMPHOID NEOPLASMS IN HUMANS (2022)

B CELL		T CELL	
<p>WHO Classification, 5th edition</p> <p>Tumour-like lesions with B-cell predominance</p> <p>Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma</p> <p>IgG4-related disease</p> <p>Unicentric Castlemans disease</p> <p>Idiopathic multicentric Castlemans disease</p> <p>KSHV/HHV8-associated multicentric Castlemans disease</p> <p>Precursor B-cell neoplasms</p> <p>B-cell lymphoblastic leukaemias/lymphomas</p> <p>B-lymphoblastic leukaemia/lymphoma, NOS</p> <p>B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy</p> <p>B-lymphoblastic leukaemia/lymphoma with hypodiploidy</p> <p>B-lymphoblastic leukaemia/lymphoma with IAMP21</p> <p>B-lymphoblastic leukaemia/lymphoma with BCR-ABL1 fusion</p> <p>B-lymphoblastic leukaemia features</p> <p>B-lymphoblastic leukaemia rearrangement</p> <p>B-lymphoblastic leukaemia RUNX1 fusion</p> <p>B-lymphoblastic leukaemia features</p> <p>B-lymphoblastic leukaemia features</p> <p>B-lymphoblastic leukaemia genetic abnormalities</p> <p>Mature B-cell neoplasm</p> <p>Pre-neoplastic and neoplastic proliferations</p> <p>Monoclonal B-cell lymphocytosis</p> <p>Chronic lymphocytic leukaemia (Entity deleted)</p> <p>Splenic B-cell lymphoma</p> <p>Hairy cell leukaemia</p> <p>Splenic marginal zone lymphoma</p> <p>Splenic diffuse red pulp lymphoma</p>	<p>WHO Classification, 5th edition</p> <p>Cutaneous follicle centre lymphoma</p> <p>Primary cutaneous follicle centre lymphoma</p> <p>Mantle cell lymphoma</p> <p>In situ mantle cell neoplasm</p> <p>Mantle cell lymphoma</p> <p>Leukaemic non-nodal mantle cell lymphoma</p> <p>Transformations of indolent B-cell lymphomas</p> <p>Transformations of indolent B-cell lymphomas</p> <p>Large B-cell lymphomas</p> <p>Diffuse large B-cell lymphoma, NOS</p> <p>T-cell/histiocyte-rich large B-cell lymphoma</p> <p>Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements</p> <p>AI Kaposi's large B-cell lymphoma</p>	<p>WHO Classification, 5th edition</p> <p>Tumour-like lesions with T-cell predominance</p> <p>Kikuchi-Fujimoto disease</p> <p>Indolent T-lymphoblastic proliferation</p> <p>Autoimmune lymphoproliferative syndrome</p> <p>Precursor T-cell neoplasms</p> <p>T-lymphoblastic leukaemia/lymphoma</p> <p>T-lymphoblastic leukaemia / lymphoma, NOS</p> <p>Early T-precursor lymphoblastic leukaemia / lymphoma (Entity deleted)</p> <p>Mature T-cell and NK-cell neoplasms</p> <p>Mature T-cell and NK-cell leukaemias</p> <p>T-prolymphocytic leukaemia</p> <p>T-large granular lymphocytic leukaemia</p>	<p>Extranodal NK/T-cell lymphoma</p> <p>EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood</p> <p>Severe mosquito bite allergy</p> <p>Hydroa vacciniforme lymphoproliferative disorder</p> <p>Systemic chronic active EBV disease</p> <p>Systemic EBV-positive T-cell lymphoma of childhood</p>
<p>Lymphoplasmacytic lymphoma</p> <p>Lymphoplasmacytic lymphoma</p> <p>Marginal zone lymphoma</p> <p>Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue</p> <p>Primary cutaneous marginal zone lymphoma</p> <p>Nodal marginal zone lymphoma</p> <p>Paediatric marginal zone lymphoma</p> <p>Follicular lymphoma</p> <p>In situ follicular B-cell neoplasm</p> <p>Follicular lymphoma</p> <p>Paediatric-type follicular lymphoma</p> <p>Duodenal-type follicular lymphoma</p>	<p>KSHV/HHV8-positive diffuse large B-cell lymphoma</p> <p>KSHV/HHV8-positive geminotropic lymphoproliferative disorder</p> <p>Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation</p> <p>Hyperplasia arising in immune deficiency/dysregulation</p> <p>Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation</p> <p>EBV-positive mucocutaneous ulcer</p> <p>Lymphomas arising in immune deficiency / dysregulation</p> <p>Inborn error of immunity-associated lymphoid proliferations and lymphomas</p>	<p>Intestinal T-cell lymphoma, NOS</p> <p>Hepatosplenic T-cell lymphoma</p> <p>Hepatosplenic T-cell lymphoma</p> <p>Anaplastic large cell lymphoma</p> <p>ALK-positive anaplastic large cell lymphoma</p> <p>ALK-negative anaplastic large cell lymphoma</p> <p>Breast implant-associated anaplastic large cell lymphoma</p> <p>Nodal T-follicular helper (TFH) cell lymphoma</p> <p>Nodal TFH cell lymphoma, angioimmunoblastic type</p> <p>Nodal TFH cell lymphoma, follicular type</p> <p>Nodal TFH cell lymphoma, NOS</p> <p>Other peripheral T-cell lymphomas</p> <p>Peripheral T-cell lymphoma, not otherwise specified</p> <p>EBV-positive NK/T-cell lymphomas</p> <p>EBV-positive nodal T- and NK-cell lymphoma</p>	

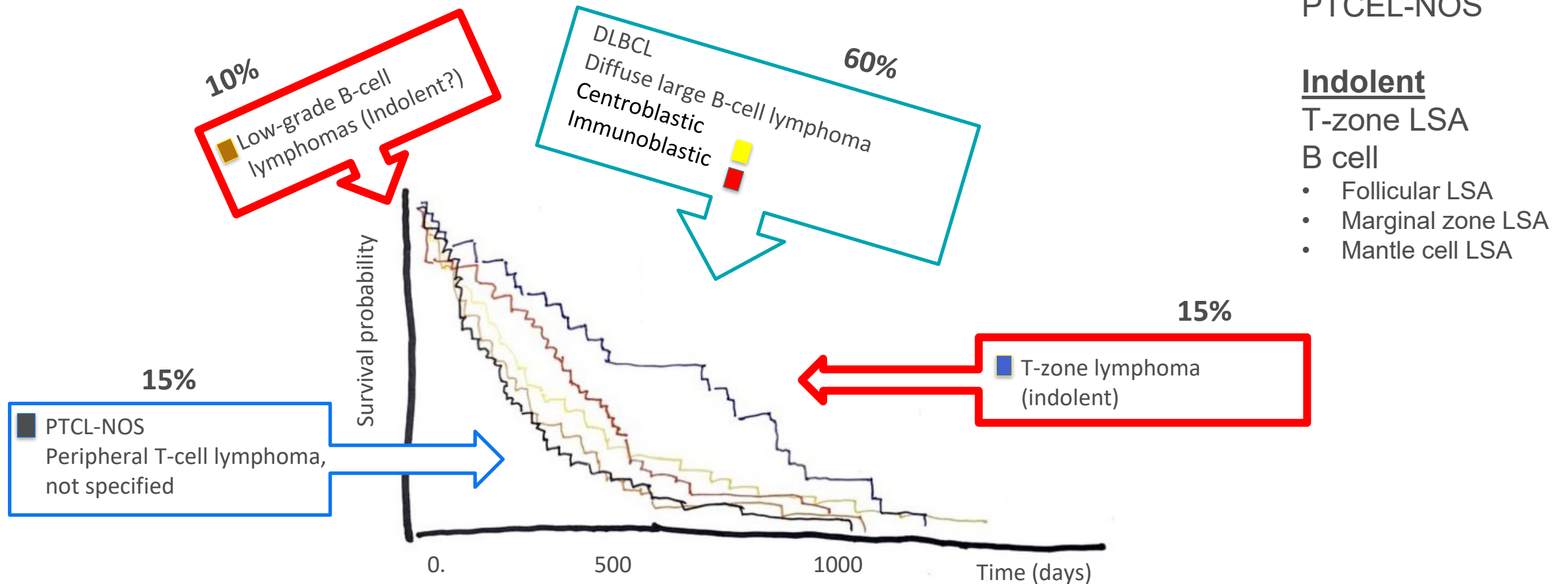
- Prognostic
- Treatment changes with histologic subtype
- Morphology, immunophenotype (IPT), genetic features and anatomic location

B Cell Neoplasms
Precursor B cell neoplasms
Precursor B lymphoblastic leukemia/lymphoma
Mature (peripheral) B cell neoplasms
B cell chronic lymphocytic leukemia/prolymphocytic
Leukemia/small lymphocytic lymphoma
B cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B cell lymphoma
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue type
Nodal marginal zone lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B cell lymphoma ^a
Mediastinal large B cell lymphoma
Burkitt's lymphoma/Burkitt's cell leukemia
Provisional entity: high-grade B cell lymphoma
Burkitt's-like ^a
Primary effusion lymphoma
T Cell and Putative Natural Killer Cell Neoplasms
Precursor T cell neoplasm
Precursor T lymphoblastic
Lymphoma/leukemia
Mature (peripheral) T cell and natural killer cell neoplasms
T cell prolymphocytic leukemia
Large granular lymphocyte leukemia (LGL)
Aggressive natural killer (NK) cell leukemia
Peripheral T cell lymphomas, unspecified ^a
Adult T cell lymphoma/leukemia
Intestinal T cell lymphoma (±enteropathy associated)
Hepatosplenic γδT cell lymphoma
Subcutaneous panniculitis-like T cell lymphoma
Mycosis fungoides/Sézary syndrome
Anaplastic large cell lymphoma, T and null cell primary cutaneous type
Peripheral T cell lymphoma not otherwise specified
Angioimmunoblastic T cell lymphoma
Angiocentric T cell lymphoma

(Vet Pathol; Valli et al. 2011)

WHO classification of K9 multicentric lymphoma and prognosis: what do we know?

Association between WHO classification type, disease stage, tumor subtype, mitotic rate and treatment with survival in 456 dogs!!



(Vet Pathol; Valli et al. 2013)

Morphologic classification of canine lymphomas and prognosis: what do we know?

What is all this fuss about??

Isn't it "B for Bad and T for Terrible" when it comes to TREATMENT??

Traditional thinking: ~~Prognosis depends on the treatment~~

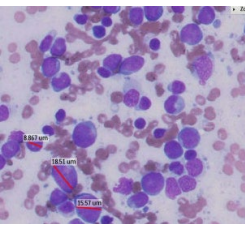
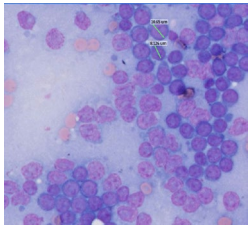
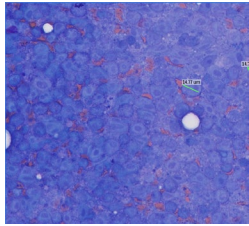
Current evidence:

- **PROGNOSIS** depends on lymphoma type (WHO)
- Need of **SPECIFIC THERAPIES**

Isn't it that histology is needed for classification?

WHO classification of K9 multicentric lymphoma and prognosis: what do we know?

B-cell lymphomas

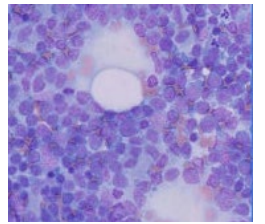
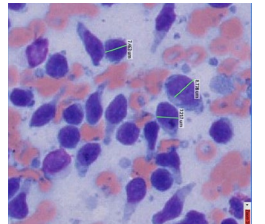
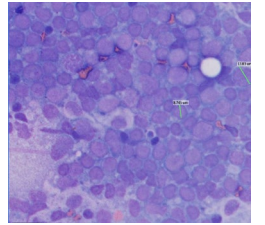


- **Diffuse large cell lymphoma**
 - Centroblastic
 - Immunoblastic
 - Anaplastic
- T-cell rich B-cell lymphoma
- **Marginal cell lymphoma (I)**
- **Follicular lymphoma (I)**
- Lymphoblastic B-cell lymphoma

(Pics credit: Dr Wheeler)

T-cell lymphomas

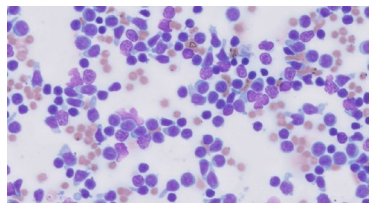
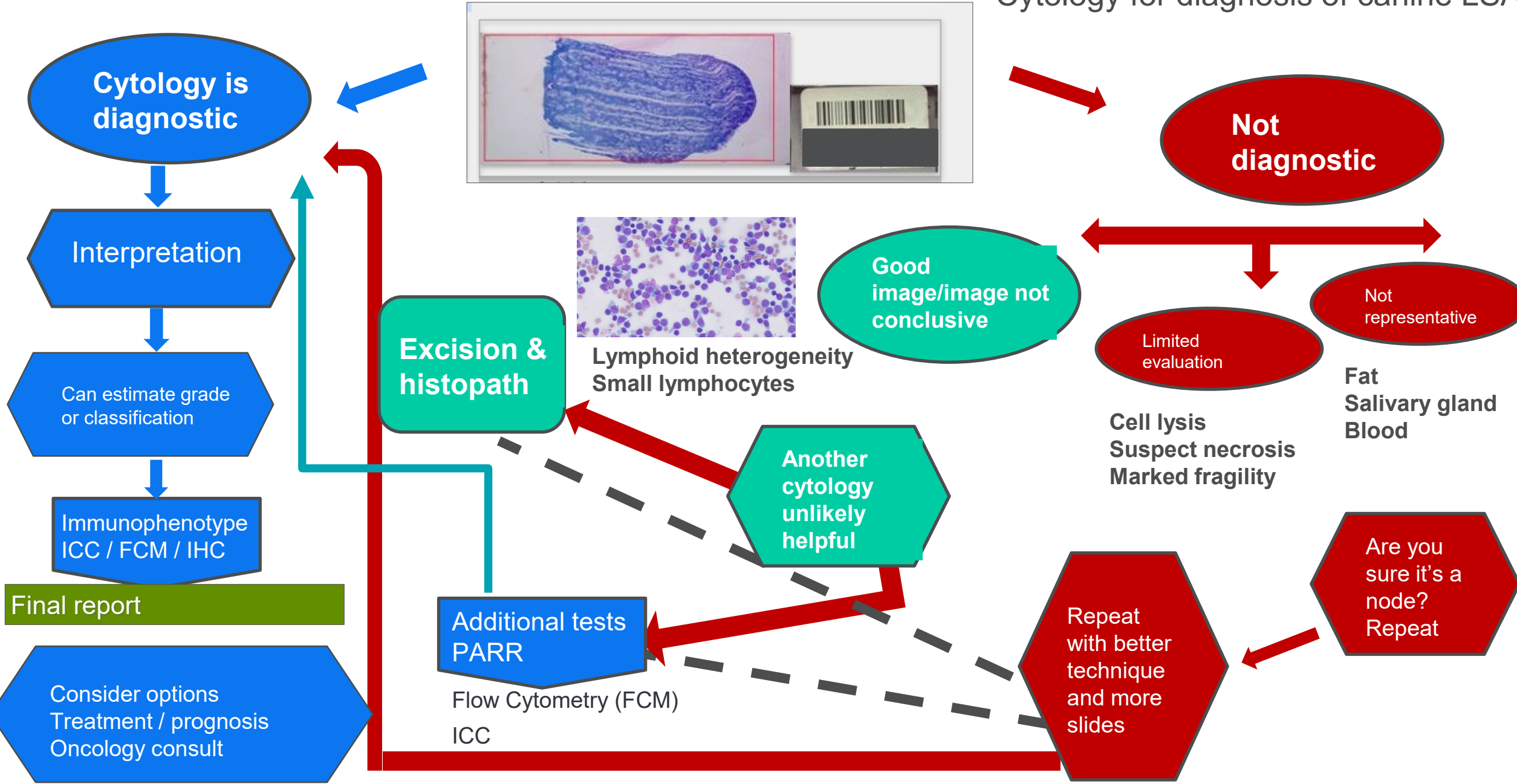
- Lymphoblastic T-cell lymphoma
- **Peripheral T-cell lymphoma, not specified**
- **T-Zone lymphoma (I)**
- T-cell lymphoma associated enteropathy
- Mycosis fungoides
- Hepatosplenic T-cell lymphoma
- T-cell lymphoma associated with panniculitis



(I=indolent)

Entities recognized by the ACVP lymphoma working group.

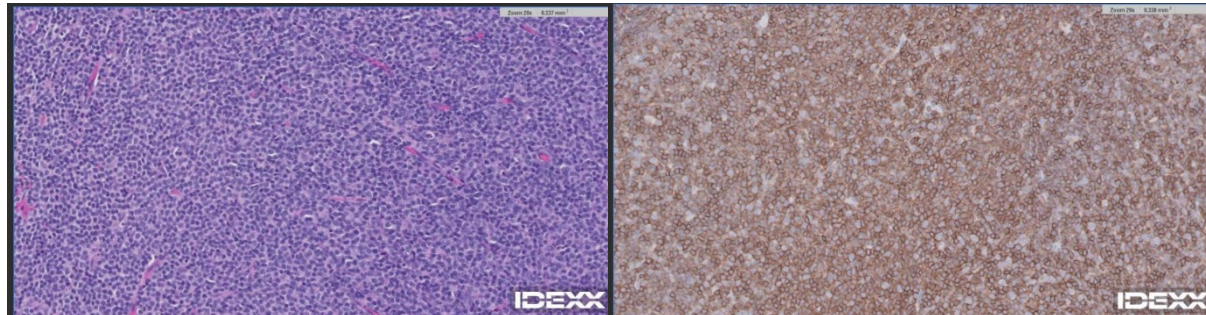
Cytology for diagnosis of canine LSA



(Scheme credit: Dr Wheeler; IDEXX)

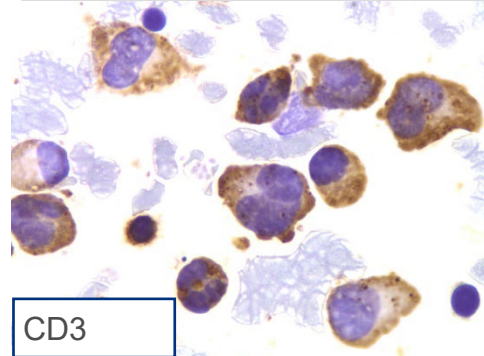
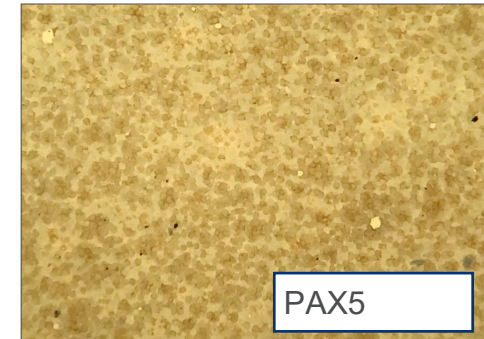
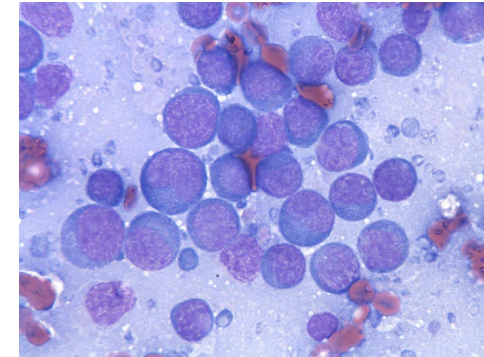
Non indolent multicentric canine lymphoma

- **Diffuse large B-cell lymphomas (DLBCL) - 60%**
- **Peripheral T cell LSA- not otherwise specified (PTCL_NOS) - 15%**
- Called non indolent as often high grade = rapid progression/dissemination
- Easy to diagnose with cytology plus ancillary tests
 - Flow cytometry/immunocytochemistry
- Histology + immunohistochemistry
- B-cell traditionally treated with CHOP / COP protocols - ↓ remissions
- New protocols: LOPP - improved results for T-cell



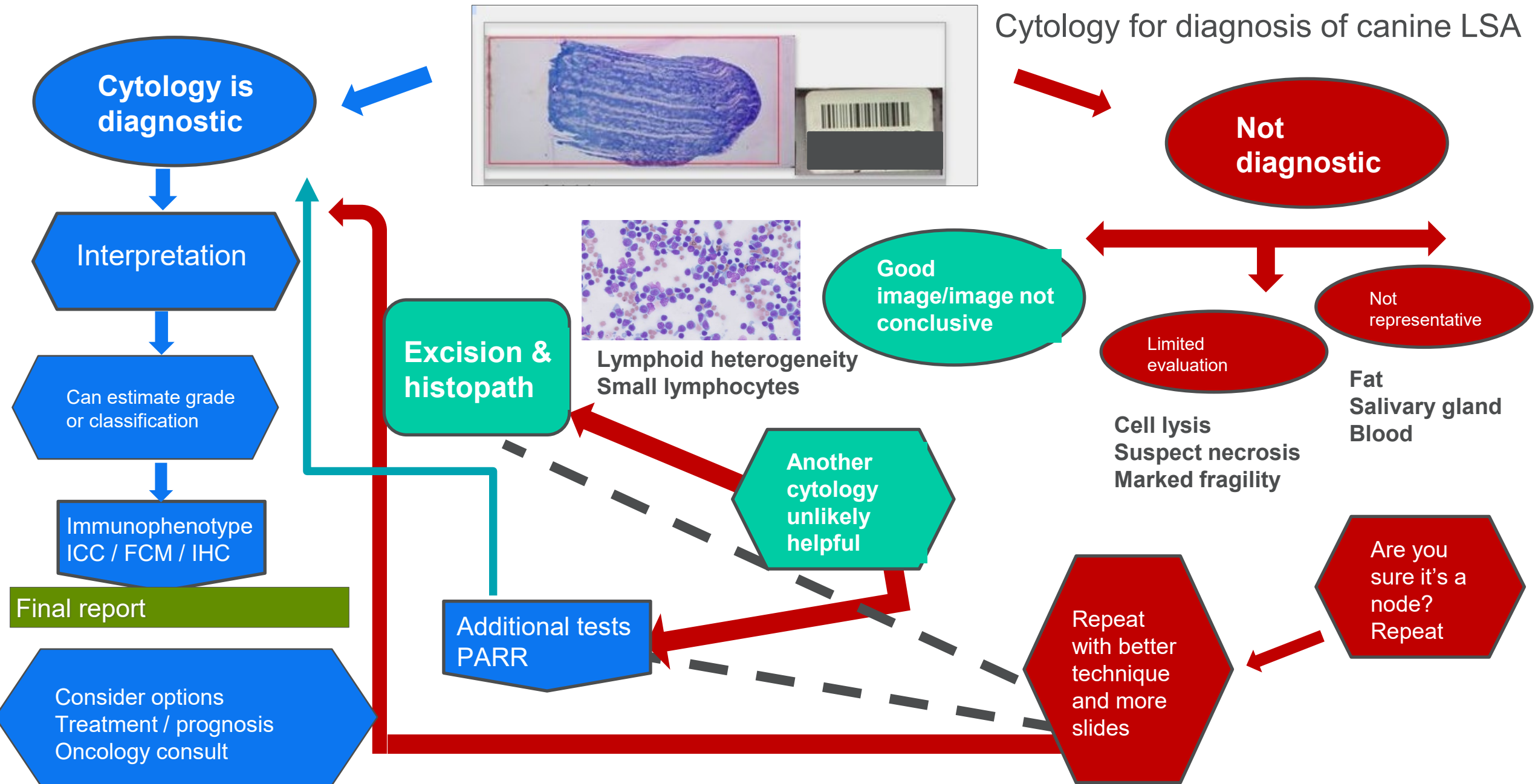
(Credits: IDEXX)

(Valli et al. 2013; Vail et al. 2020)



(Credits: Dr CG Couto IDEXX and Nazaré Pinto da Cunha, Cedivet)

Cytology for diagnosis of canine LSA



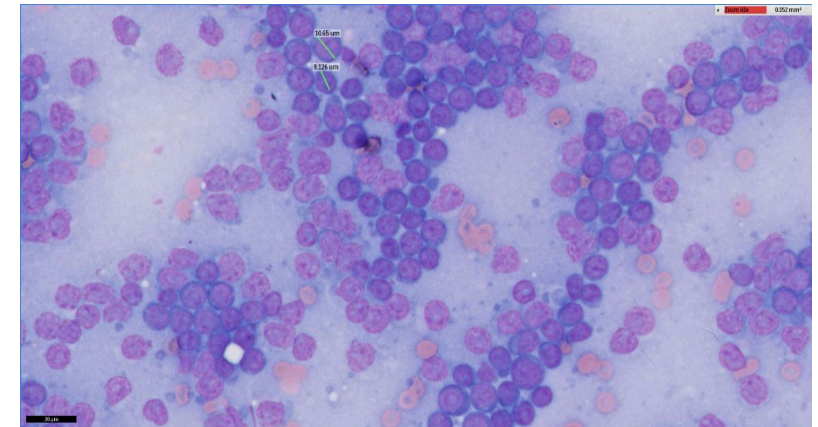
Indolent multicentric canine lymphoma

- Associated to slow progressing behaviour, often despite therapy
- Sometimes Stage I – lymph node removal diagnostic & therapeutic

B cell type: Follicular, Marginal zone and Mantle cell LSA

- Heterogeneity on cytology → histology needed + IHC or PARR
 - Solely splenic – surgery curative in most cases
 - Nodal: clinical behaviour less understood
 - More specific literature needed

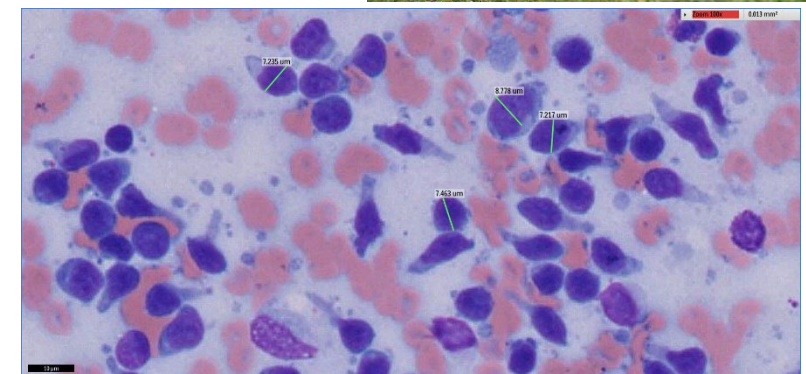
(Flood-Knapik et al. 2013; Marconato et al. 2019)



(Pics credit: Dr Wheeler)

T cell type: Canine multicentric T-zone Lymphoma

- **Indolent** form of LSA – slow progression with or without therapy – 15%
- 60% have peripheral lymphocytosis – no impact in prognosis
- Diagnosis with histology – recommended for stage I
- Cytology +Flow cytometry – distinctive profile
- Long median survival times - around 2 years! even without treatment!
- Periodic monitoring / treatment **only** with clinical signs
 - lymph nodes' size
 - lymphocytosis progressing
- Many dogs do not get in remission with treatment!
 - Non aggressive oral protocols
 - **Prednisolone and chlorambucil (alkylating agents)**



(J Vet Int Med. Seeling et al. 2014; Martini et al. 2016)

(Pics credit: Dr Wheeler)

Wrap up

- Morphologic classification of canine multicentric lymphoma provides prognostic information and guides therapy
 - WHO classification or as a minimum estimation of grade plus immunophenotype
- Histopathology with IHC allows subclassification of all canine lymphomas
- When diagnosed on cytology, ICC and FCM can allow classification of non-indolent lymphomas
- For T-zone lymphoma (indolent) histology or cytology plus flow cytometry is diagnostic
- Histopathology is needed for the diagnosis of indolent B-cell lymphoma
 - Follicular lymphoma, marginal zone and mantle cell lymphoma

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Questions?

