



Lymphoma

Diagnosis & Treatment

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Introduction

What is lymphoma?

Why to animal get lymphoma?

Diagnosis

- Staging
- Prognostic indicators

Treatment options

- Steroids
- Chemotherapy



What is Lymphoma

Cancer of lymphocytes (white blood cells)

Lymphosarcoma / malignant lymphoma

One of the most common canine neoplasms

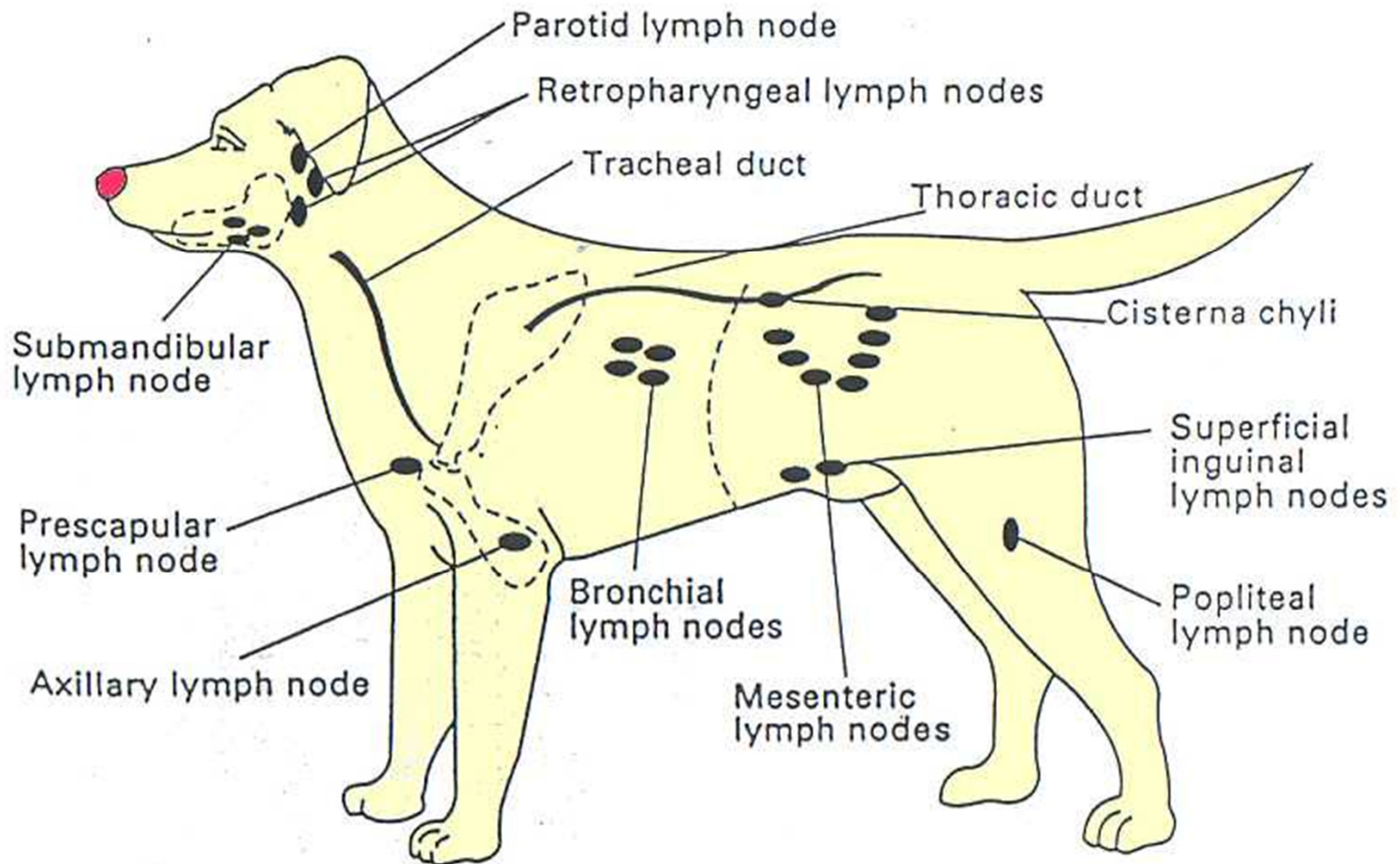
- Incidence 114 cases a year per 100,000 dogs¹
- Incidence increases with age
 - <1 year old 1.5 cases per 100,000 dogs
 - 10-11 year olds 84 cases per 100,000 dogs

Incidence in cats proportional to FeLV

Estimated 2% of referral institution caseload



Lymph Node Positions



Canine Lymphoma

Histological classification

- 66% high grade
- 28% intermediate grade
- 6% low grade

Anatomical classification

- Multicentric 84%
- Alimentary $\leq 7\%$
- Extranodal $\leq 7\%$
- Mediastinal $\leq 2\%$

Sub-types

- B-cell
 - Diffuse/multi-centric
 - T-cell-rich large B-cell
 - Marginal zone/low-grade
- T-cell
 - Diffuse/multi-centric
 - T-zone
 - Extranodal
 - Cutaneous
- Null-cell



What causes Lymphoma?

Genetic factors

- Breed predispositions
 - ↑ Risk: Boxers / Bassets / St Bernard's / Scotties / Airedales
 - ↓ Risk: Dachshunds / Pomeranians / Yorkies
- Chromosomal abnormalities

Environmental

- Urban vs Rural
- Herbicides
- Magnetic fields
- Tobacco smoke

Infectious causes

- FeLV / FIV



Feline Leukaemia Virus

FeLV causes Lymphoma in cats

Incidence markedly reduced with vaccination

- Pre vacc 60-70% lymphoma FeLV +
- Post vacc 10-20% lymphoma FeLV +

FeLV gives rise mostly to multi-centric & mediastinal LSA

FeLV seen in younger cats

Decreased incidence changed pattern of LSA in cats



Feline Lymphoma

Site	Frequency	Age	T-Cells	FeLV
GIT	50-70%	10 - 14	High	Low (5%)
Multicentric	10-25%	α to FeLV	α to FeLV	Approx 1/3
Thymic	10-20%	Young	High	High >80%
Nasal	10%	Aged	Low	Low
Renal	5-10%	Middle age	Low	Low-Mod
Other	5-25%	Mixed	Mixed	Mixed



Clinical Signs

- Enlargement of lymphoid tissue
 - Lymph node enlargement
 - Lymphadenopathy
 - Splenic enlargement
 - Splenomegaly
 - Hepatic enlargement
 - Hepatomegaly



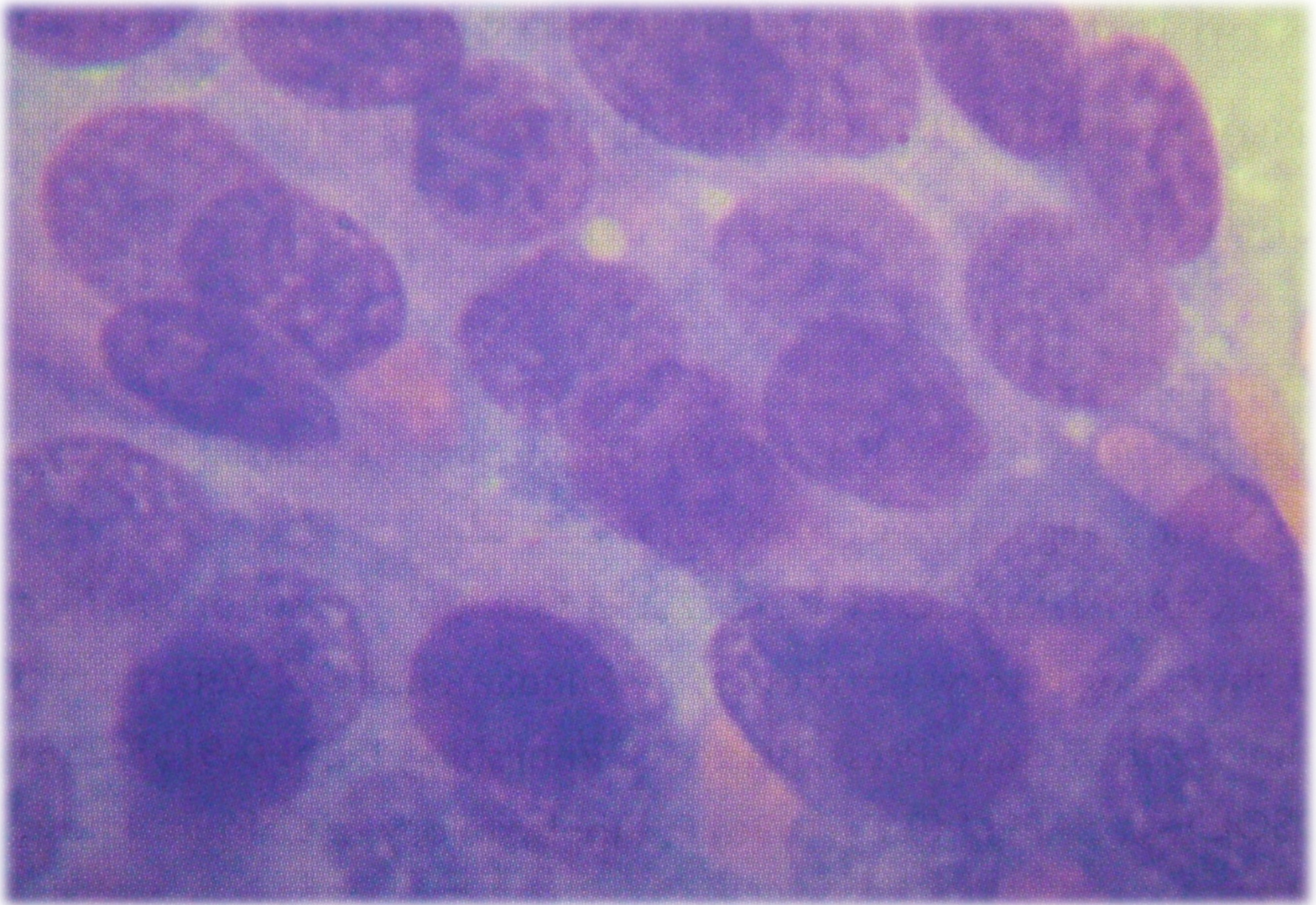


Clinical Signs

Reduced function of normal tissue

- Bone marrow involvement
 - Anaemia
 - Decreased platelets (thrombocytopenia)
 - Decreased neutrophils (neutropenia)
- Gastrointestinal Lymphoma
- CNS Lymphoma
- Renal Lymphoma
- Mediastinal Lymphoma
- Cutaneous Lymphoma
 - Mycosis Fungoides
- Ocular Lymphoma





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Adjunctive Tests

Histopathology

Immuno-histochemistry

B-cells **CD79a** / T-cells **CD3+**

Thymidine Kinase

Enzyme needed for cell division & not normally released into serum

Increased levels specific for LSA

PARR

Test of T-cell clonality

Blood Lymphocytes + in grade III LSA

Not correlated to Prognosis



Markers of a Poorer Prognosis

WHO stage V

Sub-stage b

T cells

Hypercalcaemia

Pre-treatment with steroid

Males

High proliferation rate

Cranial mediastinal mass

High histology grade



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WHO Staging

Stage I

Single LN

Stage II

Multiple LNs in one area

Stage III

Generalised lymphadenopathy

Stage IV

Generalised lymphadenopathy

Liver and spleen involvement

Stage V

Bone marrow involvement or non lymphoid organ involvement e.g. CNS



Sub-Stages

a – Well / no clinical signs

b – Ill / clinical signs



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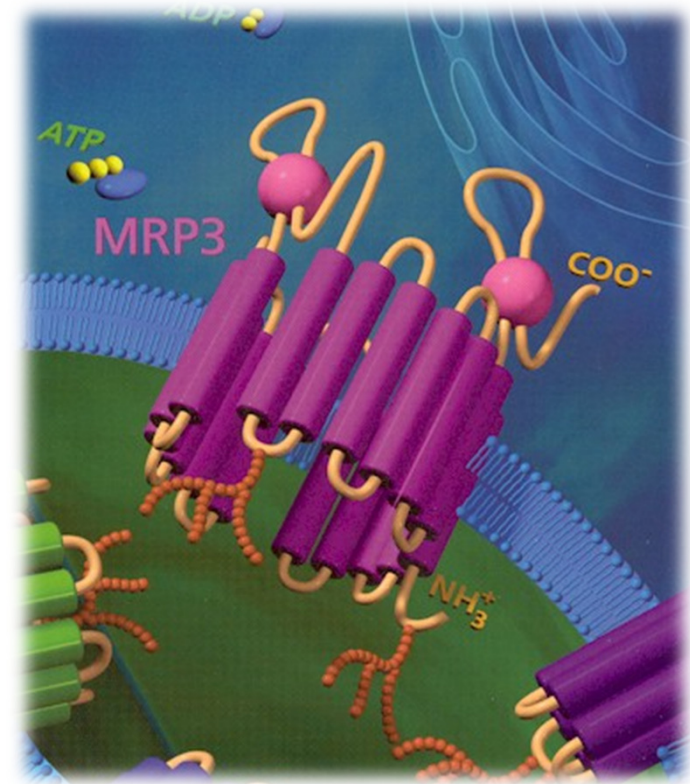
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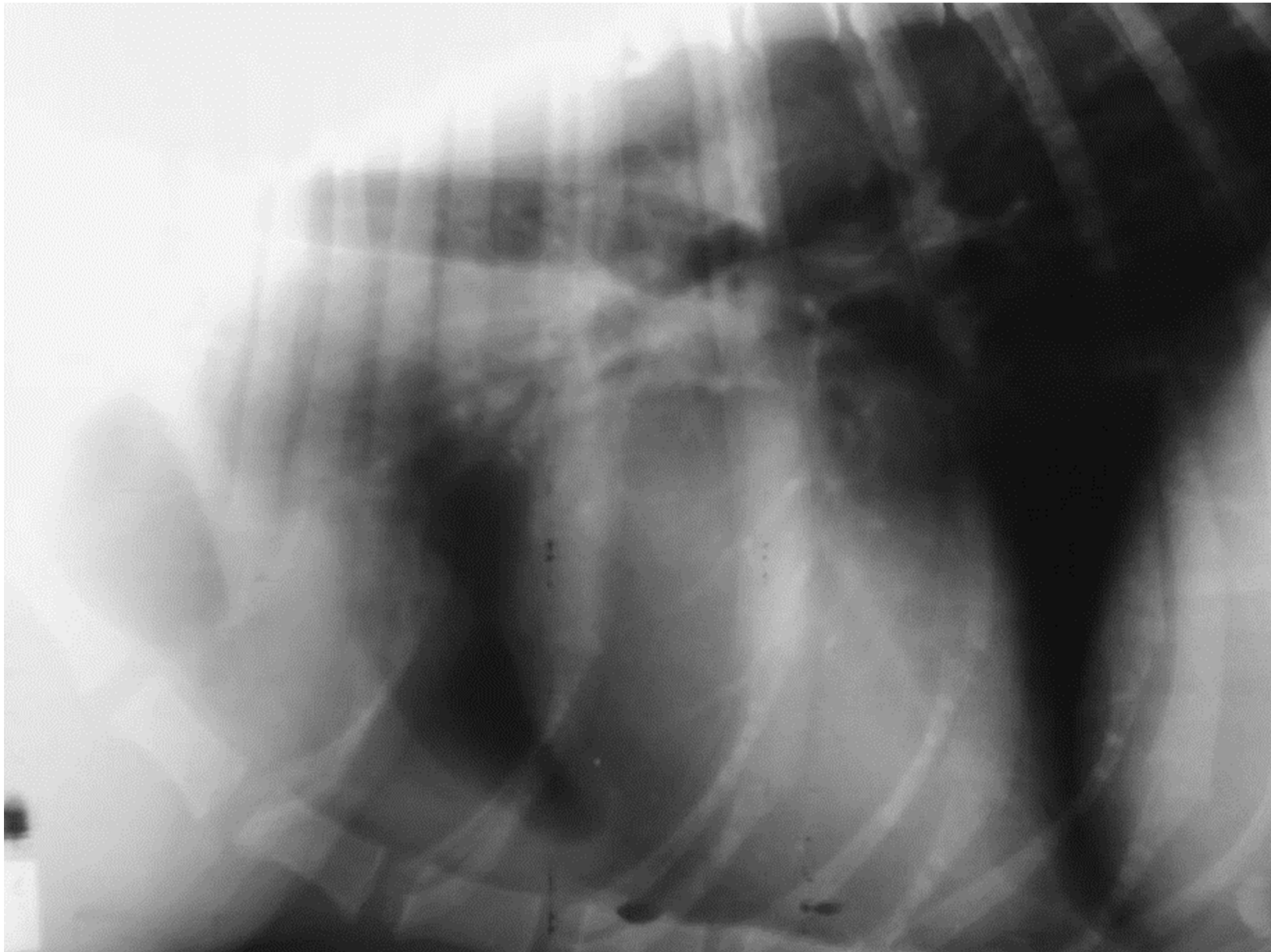
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Treatment

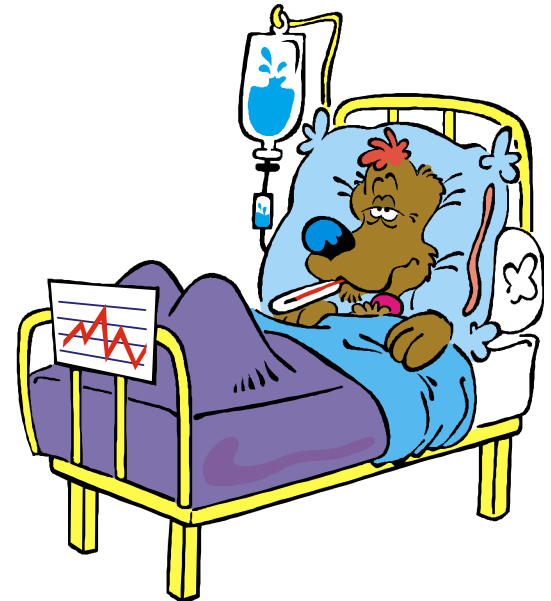
Untreated dogs succumb in 4-6 weeks

Lymphoma is very responsive to chemotherapy

- 90% of dogs will respond
- 70% of cats will respond

Median survival time (MST) depends on protocol

- Steroids alone – 8-12 weeks
- COP – 6 months
- Doxorubicin alone – 7 months
- Madison-Wisconsin – 12-18 months



Chemotherapy

- Lymphoma is a systemic disease therefore systemic treatment
- Lymphoma is very responsive to chemotherapy
- Chemotherapy drugs damage DNA
 - Preventing cell division or inducing apoptosis
 - Affects cells dividing quickest the most
 - Affects neoplastic cells more than normal cells as they often lack repair mechanisms
- Chemotherapy well tolerated in animal at doses utilised
 - Used to palliate clinical signs rather than cure disease
 - 90% of owners would treat a dog again with chemotherapy for lymphoma if placed in the same situation



Safety of Chemotherapy

Occupational Exposure is Significant

- Human nurses increased levels in urine
- Similar exposure also seen in veterinarians
- Reduce administration risks by:
 - Wear protective clothing
 - Used laminar flow cabinet for reconstitution
 - Dispose of waste appropriately

Risks to Owners

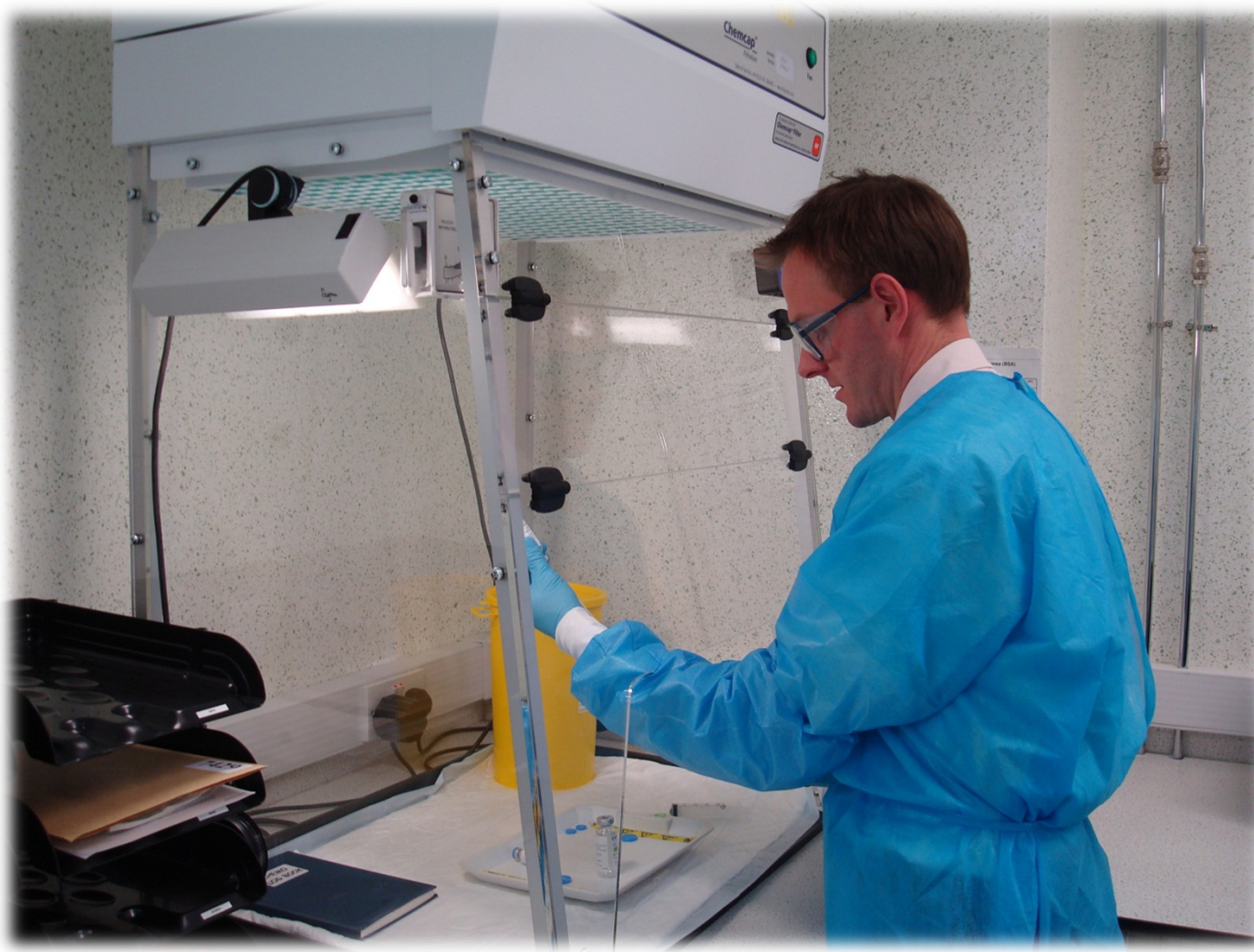
- Excretion in Faeces and Urine dependant on the agent used
 - Care clearing up for first 72 hours
- Not to handle tablets directly
- Risks greatest in pregnancy / immuno-suppressed
 - e.g. HIV+ or Elderly owners



Giving Chemotherapy



Preparing Chemotherapy



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Giving Chemotherapy



Which is the best drug to use?

- All drugs induce drug resistance, combinations reduce the speed this occurs
- Combinations of drugs that work in different ways, increases the number of cells targeted when the population is varied
- Owners wishes / expectations very important as well as efficacy
 - Costs vary widely
 - 12 months of treatment with COP \approx £1500-2000
 - Full 25 Week Madison-Wisconsin protocol \approx £3-4000
 - Some protocols very 'owner intense' with frequent visits need
 - For example fractious or aggressive animals, might be better with tablet only or single agent doxorubicin (q3 weeks)
- CNS disease need to use drugs which cross the BBB
 - CCNU / Cytarabine



How frequently do I give the drugs?

Dose Intensity Chemotherapy

Uses the maximal tolerated dose and the shortest period possible between doses

Dose reductions of 20% can reduce efficacy by up to 50%

Dosage calculated proportionally to BSA in do rather than weight (thought to more accurately reflects metabolism – although controversial in animals <15kg)

Metronomic Chemotherapy

Smaller but more frequent dosing

Targets the growing vascular supply to the tumour, thus reduces tumour growth is not very applicable to LSA (useful for HSA)



Chemotherapy for Lymphoma



Catabolic steroid

Inhibits DNA synthesis

Directly toxic to lymphocytes

Also anti-inflammatory

Cheap / well tolerated

SE PU/PD, polyphagia,
weight changes, GIT
ulceration etc



Chemotherapy for Lymphoma

Prednisolone

Vincristine

Cyclophosphamide

Doxorubicin

L-Asparaginase

CC



Derived from periwinkle

Inhibits the formation of
microtubules

These are needed for cell
division

Given by intravenously

Metabolised by the liver
excreted in faeces



Chemotherapy for Lymphoma

Prednisolone

Vincristine

Cyclophosphamide

Doxorubicin

Alkylating agent

Bind DNA & introduce an alkyl group

Stops transcription,
replication & repair

Cheap – relatively well
tolerated

Urinary excretion

SE: Haemorrhagic cystitis



Chemotherapy for Lymphoma

Prednisolone

Vincristine

Cyclophosphamide

Doxorubicin

L-Asparaginase

CCNU



Multiple actions

Intercalates DNA

Inhibits DNA replication

Inhibits protein synthesis

Forms free radicals

Given as i/v infusion

Care with catheter

SE: DCM, HS, nephrotoxic
in cats



Chemotherapy for Lymphoma

Prednisolone

Vincristine

Cyclophosphamide

Doxorubicin

L-Asparaginase

CCNU

Bacterial enzyme that
degrades asparagine

Stops cells growing

Inhibits protein synthesis

Normal cells make asp.

Resistance relatively easy
as select for cells will up
regulated asparagine
synthetase



Chemotherapy for Lymphoma

Prednisolone

V

C

D

L-Asparaginase

CCNU



Alkylating agent

Bind DNA & introduce an alkyl group

Stops transcription, replication & repair

Expensive and moderately toxic

Profoundly myelosuppressive

Hepatotoxic



COP Protocol

Cyclophosphamide, Vincristine (O – Oncovin) and Prednisolone

Most commonly used Chemotherapy protocol used in SAP for LSA

Relatively Cheap, 'easy' and well tolerated

Induction (8 weeks)

Cyclophosphamide 50mg/m² po for the 1st 4 days of each week

Vincristine 0.5mg/m² iv **q7** days

Prednisolone 40mg/m² po SID for 7 days then 20mg/m² EOD with
Cyclophosphamide



COP Protocol - Maintenance

Maintenance (2-6 months)

Vincristine 0.5mg/m² iv **q14** days

Cyclophosphamide + Prednisolone given for the first 4 days of every other week

Maintenance (6-12 months)

Vincristine 0.5mg/m² iv **q21** days

Cyclophosphamide + Prednisolone given for the first 4 days of each third week

Maintenance (12 - 18 months)

Vincristine 0.5mg/m² iv **q28** days

Cyclophosphamide + Prednisolone given for the first 4 days of each fourth week



Madison-Wisconsin Protocol

Considered the 'Gold Standard' chemotherapy for LSA

Uses Vincristine, Cyclophosphamide, Prednisolone, Doxorubicin and L-asparaginase

Many variations but standard protocol is 25wks

Drug	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Pred	●	●	●	●																					
L-Asp	●																								
Vincristine	●		●			●		●			●				●				●				●		
Cyclophos		●					●						●								●				
Doxo				●					●								●								●



Rescue Protocols

- Subsequent remissions can be achieved
 - Usually harder to achieve
 - Usually for shorter periods
- Repeating the induction protocol
 - Achieved in approx 50% of patients
 - Period of approx 50% of 1st remission
- Maintenance free protocol longer 2nd remission periods
- Rescue protocols
 - MOPP
 - Doxorubicin
 - CCNU



Complications of Chemotherapy

Drugs affect all cells in the body

Affects those dividing quickest the most

Side effects occur as a result of these cells being affected

Side effects seen in about 10% of patients

- Bone marrow – decreased white blood cells / Platelets
- Hair follicles – Dogs and cats don't loose hair (c.f. people) however whiskers sometimes fall out and hair re-growth may be poor
- GUT – vomiting and diarrhoea are common as a result of drug administration. Nausea is also common in people, but harder to recognise in animals.



Specific Complications

- Extra-vascularisation
 - Local irritation around injection site
 - Vincristine & Doxorubicin
- Haemorrhagic cystitis
 - Cyclophosphamide
 - Breakdown product Acrolein toxic to bladder
- DCM – Doxorubicin / Mitoxantrone
- Anaphylaxis/ Hypersensitivity – L-asparaginase



Any Questions?



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