



Australian and New Zealand College of
Veterinary Scientists

Fellowship Examination

June 2013

Veterinary Oncology

Paper 1

Perusal time: **Twenty (20)** minutes

Time allowed: **Four (4)** hours after perusal

Answer **ALL TEN (10)** questions

Answer **TEN** questions each worth 24 markstotal 240 marks

Paper 1: Veterinary Oncology

Answer all ten (10) questions

1. The majority of neoplastic cells have defects in regulatory circuits that govern cellular proliferation and homeostasis. These acquired characteristics have been collectively referred to as ‘The Hallmarks of Cancer’.
 - a) Explain the **six (6)** cellular characteristics originally described by Hanahan and Weinberg that result in malignant growth and explain strategies by which neoplastic cells acquire each characteristic. Include veterinary examples of **each** characteristic in your answer. *(18 marks)*
 - b) Briefly discuss the **two (2)** proposed emerging characteristics of neoplastic cells. *(6 marks)*

2. Answer **both** parts of this question:
 - a) Juxtapose competing models that may explain the complex process of metastasis. Include in your answer a definition of the steps of the metastatic cascade. *(18 marks)*
 - b) Define the following terms in regards to tumour invasion:
 - i. mesenchymal invasion *(2 marks)*
 - ii. ameboid invasion *(2 marks)*
 - iii. collective invasion. *(2 marks)*

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3. Answer **both** parts of this question:

- a) Discuss what is meant by the term ‘stem cell theory’ as it relates to oncogenesis, and using examples of neoplasms evaluated in veterinary medicine, explain how cancer stem cells may contribute to therapeutic failure. (12 marks)
- b) Define the following terms and outline how **each** relates to tumour growth and/or metastasis:
 - i. epithelial mesenchymal transition (3 marks)
 - ii. angiogenesis (3 marks)
 - iii. vasculogenesis (3 marks)
 - iv. vascular mimicry. (3 marks)

4. Answer **all** parts of this question:

- a) List the **five (5)** primary classes of oncogenes. (5 marks)
- b) Discuss the roles of oncogenes and tumour suppressor genes in the development of neoplasia. In your answer, please define key terms and use specific examples (human and veterinary where appropriate) to explain how oncogenes become activated. (16 marks)
- c) Under normal conditions, p53 is activated following cellular DNA damage. Name **three (3)** ways in which a loss of functional p53 can occur. (3 marks)

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5. The cell cycle is the series of events that take place in a cell leading to its division and duplication (replication).
- a) In a few sentences, define the term ‘restriction point’ and explain the role the retinoblastoma protein (Rb) plays in regulating this phase of the cell cycle. *(3 marks)*
 - b) Describe the interaction between cyclins and cycle dependent kinases with respect to the cell cycle. *(3 marks)*
 - c) Describe the function and site of action of cyclin dependent kinases inhibitors. Include in your answer an example of **each** of the **two (2)** known families. *(3 marks)*
 - d) Discuss ways in which neoplastic cells can uniquely exploit the cell cycle. *(15 marks)*
6. Answer **all** parts of this question:
- a) Differentiate apoptosis and necrosis. *(4 marks)*
 - b) Describe the process of apoptosis, indicating how neoplastic cells may avoid apoptosis. *(16 marks)*
 - c) Briefly describe the significance of the bcl-2: bax ratio. *(4 marks)*

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7. In order to understand the pathology of cancer, one must have a strong understanding of many key terms.

Answer **all** parts of this question:

a) Define the following terms: (5 marks)

- i. hyperplasia
- ii. atrophy
- iii. metaplasia
- iv. dysplasia
- v. in situ.

b) The histopathologic 'grading' of tumours may confer important prognostic information. Identify features present on routine hematoxylin and eosin (H & E) staining that could be used to grade a tumour and give **six (6)** examples of **canine neoplasms** where 'grade' is considered of prognostic significance.

(12 marks)

c) Name the cell type identified by each of the following stains: (3 marks)

- i. desmin
- ii. vimentin
- iii. cytokeratin
- iv. s100a
- v. melan A
- vi. enolase.

d) Cell markers are of diagnostic importance in the characterisation of leukocytic proliferative diseases in dogs. List cells that express the marker and for what neoplasm the marker would help identify. (4 marks)

- i. CD3ε
- ii. CD79a
- iii. CD20
- iv. MUM1/IRF4.

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8. Answer **all** parts of this question:

a) Discuss mechanisms of carcinogenesis with reference to the following concepts:
(12 marks)

- i. multistep carcinogenesis
- ii. field cancerization
- iii. epigenetic changes
- iv. silencing of gene expression.

b) Identify carcinogens associated with **each** of the following tumours: (6 marks)

- i. mesothelioma
- ii. transitional cell carcinoma
- iii. gastric carcinoma
- iv. haemangiosarcoma
- v. lymphoma
- vi. sinonasal tumours.

c) Define the term 'chemoprevention' and differentiate types of chemopreventative agents based on their primary sites of action. (6 marks)

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9. One of the main reasons for chemotherapy failure in the treatment of cancer is the development of drug resistance by neoplastic cells.

Answer **all** parts of this question:

- a) Briefly explain the Goldie Coleman theory. (6 marks)
- b) Explain why combination chemotherapy protocols are theoretically superior to single agent protocols and describe the main objectives in such a protocol. (6 marks)
- c) Give an example of a cancer in animals where combination chemotherapy is superior to single agent therapy, and a cancer where superiority has not been observed. (4 marks)
- d) Discuss the advantages and disadvantages of:
- i. adjuvant chemotherapy (4 marks)
 - ii. neoadjuvant chemotherapy (4 marks)
10. Discuss the use of bisphosphonates in veterinary oncology including indications for their use, their mechanism of action, reported benefits of treatment, surrogate markers that have been used in clinical studies to evaluate effects on canine patients, and potential adverse effects. (24 marks)

End of paper



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Paper 2

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Answer **ALL TEN (10)** questions

Answer **TEN** questions each worth 24 markstotal 240 marks

Paper 2: Veterinary Oncology

Answer all ten (10) questions

1. Answer **all** parts of this question:

a) For **both** cisplatin (6 marks) **and** paclitaxel (6 marks)

Discuss:

- the drug class to which it belongs
- mechanism of action
- cell cycle specificity
- dose limiting toxicity
- mechanism(s) of drug resistance.

b) You are planning a chemotherapeutic protocol for a 10-year-old female German shepherd with stage II haemangiosarcoma following splenectomy. A colleague suggests a different protocol instead of your standard protocol:

Standard protocol: doxorubicin – 30 mg/m² on Day 1
cyclophosphamide – 50 mg/m² on Days 3 through 6
vincristine – 0.5 mg/m² on Days 8 and 15
Protocol repeats q 21 days

Test protocol: doxorubicin – 25 mg/m² on Day 1
cyclophosphamide – 150 mg/m² on Day 1
vincristine – 0.6 mg/m² on Days 1, 8 and 15
Protocol repeats q 21 days

Question 1 b) continued over page

- i. Calculate the dose intensity of **both** the standard and test protocol. *(3 marks)*
 - ii. Calculate the average relative dose intensity of the experimental protocol compared to the standard protocol. *(3 marks)*
 - iii. Briefly explain, in one or two sentences, the concept of dose intensity and explain how the calculation of dose intensity is useful in deciding between these two protocols. *(3 marks)*
 - iv. Comment on the use of combination chemotherapy in this case compared with single agent chemotherapy, including important elements for the successful use of combination therapy. *(3 marks)*
2. Statistical analysis is important for understanding and reviewing studies in the veterinary literature.
 - a) Clinical trials involving new drugs are commonly classified into phases. Define Phases 0 to IV in the validation of a novel treatment. *(15 marks)*
 - b) Define the following terms: *(9 marks)*
 - i. positive predictive value
 - ii. negative predictive value
 - iii. power of a test
 - iv. p-value
 - v. median
 - vi. Type I error
 - vii. Type II error
 - viii. sensitivity
 - ix. specificity.

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3. A five-year-old male neutered Great Dane presented for consultation of a palpable cervical mass of four months duration. The mass is eight centimetres and is moveable. The history includes a mild exercise intolerance of three months duration.

a) List your differential diagnoses for this mass. (2 marks)

b) A CT scan was performed and the report was as follows:

The right thyroid gland is small and has poor hyperattenuation/mineral attenuation on precontrast scan. The left thyroid gland is enlarged (4.5 H x 3.5 W x 10.4L cm) and has small foci of hyperattenuation on pre and post contrast scan. The mass is slightly hypoattenuating pre-contrast and similar in attenuation to surrounding muscles on post contrast scan. The left medial retropharyngeal lymph node is slightly larger and rounder than the right. Mandibular lymph nodes are symmetric. Mild mineralization of the external ear canal lining bilaterally, both ear canals are slightly narrow. Mild degenerative bone formation along the articular facet joints of the cervical spine. Gravity dependent mineral attenuating focus in the gall bladder, 0.7 cm diameter.

Several small mineral attenuating foci in the body of the stomach, the stomach is moderately fluid filled. The spleen is subjectively large but homogeneously attenuating.

Diagnostic interpretation:

1. Left thyroid carcinoma, suspect functional DDX adenoma.
2. Suspect right thyroid suppression vs primary hypothyroidism.
3. Left medial retropharyngeal lymphadenopathy DDX reactive, metastatic.
4. Cervical articular facet joint DJD.
5. Biliary cystolith, likely incidental.
6. Dietary indiscretion, consider stones, no evidence of obstruction.
7. Spleen DDX variant of sedation/anesthesia vs physiological variant, less likely infiltrative or reactive disease.

State the WHO staging scheme for thyroid tumours and identify the stage of disease in this patient. (8 marks)

Question 3 continued over page

- c) Please supply the following information with respect to canine thyroid carcinoma as a brief (number, phrase or single sentence) answer. (6 marks)
- i. the percentage of unilateral and bilateral tumours
 - ii. the incidence of functional thyroid tumours
 - iii. the incidence of functional thyroid tumours
 - iv. the percentage of thyroid tumours that are mobile
 - v. the metastatic rate at the time of diagnosis
 - vi. the metastatic rate at surgery.
- d) Discuss treatment options for invasive Stage III thyroid carcinoma in the dog, including the expected response rates and survival times for **each** modality. (8 marks)

4. Measures of tumour cell proliferation can provide prognostic information, predict response to various treatments, assess tumour control and predict survival.
- a) Describe what characteristic is assessed by **each** the following tests and, for **each** test, provide examples of cancers in veterinary medicine in which these tests have been evaluated, including the specific correlation (positive or negative):
- i. flow cytometry (4 marks)
 - ii. proliferating cell nuclear antigen PCNA (4 marks)
 - iii. Ki-67 (MIB-1) (4 marks)
 - iv. AgNOR. (4 marks)
- b) Briefly discuss the use of PARR (PCR for antigen receptor rearrangements) as a molecular diagnostic test in veterinary oncology. (8 marks)

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5. Prognostic factors are important in veterinary oncology and enable clinicians to guide clients regarding treatment and overall outcomes.
- a) For **each** of the following tumours, discuss prognostic factors and state the expected effect on survival in months.
 - i. primary lung tumour (canine) (6 marks)
 - ii. canine mammary carcinoma (6 marks)
 - iii. thyroid carcinoma (canine) (6 marks)
 - iv. feline mammary gland tumours. (6 marks)
6. You are presented with a 10-year-old male castrated pug that has multifocal mast cell tumours (five) along the dorsum, ventral abdomen, inguinal region and muzzle. The tumours range in size from 0.5 cm to 4 cm. The referral blood work was within normal limits, and three view thoracic radiographs revealed no abnormalities.
- a) The patient has multiple mast cell tumours (MCT). Based upon the literature, explain the likely impact of this finding on survival. (4 marks)
 - b) The use of abdominal ultrasound and bone marrow aspirates is somewhat controversial for the staging of MCT. Based upon the recent literature, please defend the argument that **each** of these techniques is useful for staging of MCT patients. (4 marks)
 - c) Based upon the literature, outline the effect of this patient's breed on prognosis. (4 marks)
 - d) Assuming a solitary tumour, discuss the potential prognostic significance of the location of mast cell tumours in dogs. For **each** site, identify whether the evidence based literature has proven or disproven a more aggressive phenotype. (6 marks)
 - e) A new 2-tier histological grading system (Kiupel *et al.* Vet Path 2011) has been created for mast cell tumours which identifies 'low' or 'high' grade categories. Identify criteria evaluated in this system, define characteristics of a 'high' grade MCT and relate this to median survival time. Contrast this system with results of earlier histological grading systems. (6 marks)

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7. Immunotherapy is an important mechanism for the treatment of cancer and relies on the immune system recognising inherent differences between normal cells and tumour cells.
- a) Identify **four (4)** pieces of evidence that support the role of the immune system in cancer treatment. Give an example from veterinary medicine for **each** example. *(4 marks)*
 - b) Describe mechanisms by which tumours evade the immune system of the host. *(4 marks)*
 - c) Cancer vaccines have been utilised in the treatment of neoplasia. For **each** vaccine type listed, discuss mechanism(s) of action and vaccine preparation, including advantages and challenges in vaccine manufacture.
 - i. whole cell/tumour cell lysate *(4 marks)*
 - ii. genetic anticancer vaccines *(4 marks)*
 - iii. viral-vectored vaccines *(4 marks)*
 - iv. dendritic cell vaccines. *(4 marks)*
8. Regarding the use of radiation therapy in veterinary oncology:
- a) List **six (6)** drugs which are known to be either a radiation sensitizer or a radiation protector and indicate under which category **each** falls. *(3 marks)*
 - b) Discuss advantages of **both** preoperative radiation therapy and postoperative radiation therapy. *(5 marks)*
 - c) Define the alpha/beta ratio as it pertains to radiation therapy, and explain its effect on cellular response to therapy. *(6 marks)*
 - d) Based on the principles of radiation biology, explain how the incidence of late side effects can be reduced when radiating the colon. *(2 marks)*
 - e) Define stereotactic radiation and list **four (4)** indications for stereotactic radiosurgery (SRS) in veterinary or human medicine. *(8 marks)*

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9. Answer **both** parts of this question:

- a) Discuss the impact of endocrine (hormonal), age and obesity on the development of mammary tumours in dogs. (12 marks)
- a) Discuss factors associated with an increased risk of development of osteosarcoma in dogs. (12 marks)

10. 'Cookie', a nine-year-old female spayed 33 kg crossbred dog, presented with a history of three generalised seizures in the preceding six weeks. All seizures have occurred at night and Cookie has recovered consciousness within two minutes. The owner describes her behaviour at home to be normal however there has been one episode that was not associated with a seizure where she seemed disoriented, lasting approximately one hour and she has had more difficulty climbing stairs. Her normal diet is chicken necks and dry food and she is fed twice a day. She has had no previous medical problems since being obtained as a rescue dog at approximately four months of age.

On physical exam Cookie is overweight—body score 4/5. No other abnormalities found.

On neurologic exam, Cookie is alert and normally responsive and no abnormalities are found.

- a) Outline your approach to diagnostic testing and/or treatment at this time. (4 marks)
- b) Comment briefly on cerebrospinal fluid analysis as a diagnostic procedure in this case. (2 marks)

A brain MRI returns the following findings:

Sagittal T1, dorsal T2 and diffusion weighted images and transverse gradient echo images were obtained through the brain with post gadolinium dorsal and sagittal T1W images and post gadolinium FLAIR transverse images.

The study demonstrates a durally based enhancing mass lesion arising from the left frontal convexity measuring 17x10x16 mm (LxWxH). This is isointense to brain on both T1 and T2 W images and shows moderate enhancement after gadolinium with a small dural tail. Adjacent to the mass there is marked hyperintensity on T2 (presumed oedema) in the brain substance and the L ventricle is compressed with some midline shift to the R side. The cerebral ventricles are not dilated. There are no other abnormalities identified.

Question 10 continued over page

- c) Based on your interpretation of this report, explain the most likely diagnosis. *(2 marks)*
- d) Based on the most likely diagnosis from the clinical presentation described, relate current classification systems and available cytological markers of malignancy to prognosis. *(8 marks)*
- e) Describe treatment options for the condition identified in c) above. *(8 marks)*

End of paper