

VCS Oncology-Pathology Working Group
Summary and Subgroup recommendation for
Histopathologic classification of canine prostate cancer

Species/Tumor: *CANINE PROSTATE CANCER SUBGROUP*

Subgroup Chairs:

1. Chair: Chiara Palmieri, Associate Professor in Veterinary Pathology, School of Veterinary Science, The University of Queensland (DVM PhD DECVP – Anatomic)/
c.palmieri@uq.edu.au

2. Co-Chair: William TN Culp, ACVS Founding Fellow of Surgical Oncology, ACVS Founding Fellow of Minimally Invasive Surgery, Professor, University of California-Davis, School of Veterinary Medicine(VMD, DACVS – Surgical Oncology)/
wculp@ucdavis.edu

Subgroup Members:

Oncologists:

Carlos Eduardo Fonseca-Alves, Assistant Professor in Small Animal Internal Medicine, Institute of Health Sciences, Paulista University - UNIP (DVM, MSc, PhD – Oncology)

Pathologists:

Robert A Foster, BVSc, PhD, MANZCVS, DACVP-anatomic. Professor, Department of Pathobiology, Ontario Veterinary College, University of Guelph.

Valeria Grieco, Associate Professor, Veterinary Pathology, Department of Veterinary Medicine, Università degli Studi di Milano (DVM, PhD)

Geoffrey Wood, Associate Professor, Pathobiology, and Assistant Co-Director, Institute for Comparative Cancer Investigation, Ontario Veterinary College, University of Guelph (DVM, PhD, DVSc)

Renee Laufer Amorim, Associate Professor, Veterinary Pathology, School of Veterinary Medicine and Animal Science (FMVZ), UNESP (DVM, MSc, PhD)

This consensus is submitted by: Chiara Palmieri

On (date): Initial – 12OCT2018, EC Review – 8SEP2019, Revised – 23DEC2019, EC Review 2 – 8APR2020

CONSENSUS:

Based on review of the literature listed below, the Canine Prostate Cancer Subgroup has concluded and recommends the following regarding **histopathologic classification** of canine prostate cancer.

Conclusions:

- All the members agree that the classification of canine prostate cancer currently adopted (Kennedy et al., 1998) does not fully recapitulate the different growth patterns and subtypes that may occur and are currently observed in histologic specimens. The WHO Classification of Tumors of Human Prostate Cancer (WHO “blue book”, 2016) and adapted to canine cancers by Lai et al. (2007) and Palmieri et al. (2014) may be used, although all the members are aware that further studies are required to validate this new system.
- When a carcinoma is known to arise in the pelvic urethra near the prostate or within the prostate itself, the differentiation between prostatic carcinoma and urothelial carcinoma (UC) should be evaluated by immunohistochemistry for uroplakin III (UPIII), and eventually with any other verified markers of prostatic or urothelial phenotype; androgen receptor (AR) and cytokeratin 7 (CK7) may be helpful. The usefulness of prostate-specific membrane antigen (PSMA) and arginine esterase (AE) is questionable.
- Until additional studies are performed to validate the new histopathologic classification, both the traditional (Kennedy et al., 1998) and the new (Lai et al., 2008; Palmieri et al., 2014) classifications based on the human WHO system (Moch et al., 2016) should be reported for all canine prostate neoplasms examined after radical prostatectomy or other biopsy techniques. All diagnostic pathologists should be familiar with the morphologic criteria for each classification system (appendix).

Future directions / Recommended studies –

- 1) Further investigation into the value of immunohistochemical markers in addition to routine histopathology is warranted. In particular, a better definition of the staining pattern of AR, CK7, and UPIII in a representative number of normal and neoplastic samples may be beneficial. The role of AE in the diagnostic differentiation between prostatic carcinoma and urothelial carcinoma requires further analysis.
- 2) The clinical relevance of currently published literature is critically hindered by the lack of relevant data (e.g. clinical signs, neutered status, survival rate, follow-up). Future studies need to include appropriate clinical outcome in order to add useful prognostic information to the classification system and support the importance of grading for differentiating pre-malignant, low-grade and high-grade prostate cancer.

Literature cited:

1. Leav I, Ling GV. *Adenocarcinoma of the canine prostate*. *Cancer* 1968; 22: 1329-1345
2. Cornell KK, Bostwick DG, Cooley DM, Hall G, Harvey HJ, Hendrick MJ, Pauli BU, Render JA, Stoica G, Swett DC, Waters DJ. *Clinical and Pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases*. *Prostate* 2000; 45: 173-183.
3. LeRoy BE, Nadella MVP, Toribio RE, Leav I, Rosol TJ (2004) *Canine prostate carcinomas express markers of urothelial and prostatic differentiation*. *Vet Pathol*, 41: 131-140.
4. Lai CL, van den Ham R, van Leenders G, van der Lugt J, Mol JA, Teske E. *Histopathological and immunohistochemical characterization of canine prostate cancer*. *Prostate*, 2008, 68(5): 477-488.
5. Palmieri C, Lean FZ, Akter SH, Romussi S, Grieco V. *A retrospective analysis of 111 canine prostatic samples: histopathological findings and classification*. *Res Vet Sci*, 2014; 97: 568-573.
6. Akter SH, Lean FZ, Lu J, Grieco V, Palmieri C. *Different growth patterns of canine prostatic carcinoma suggests different models of tumor-initiating cells*. *Vet Path* 2015,52(6), 1027-1033.
7. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO classification of tumours, of the urinary system and male genital organs*. Fourth edition. IARC, 2016.
8. Kennedy PC, Cullen JM, Edwards JF, Goldschmidt MH, Larsen S, Munson L, et al. 1998. *Histopathological Classification of Tumors of the Genital System of Domestic Animals*. WHO International Histopathological Classification of Tumors of Domestic Animals, second series. Vol. 4. American Registry of Pathology, AFIP: Washington DC, pp.21-22.

LITERATURE REVIEWED

1. Leav I, Ling GV. Adenocarcinoma of the canine prostate. *Cancer* 1968; 22: 1329-1345

Study Objective – Characterize canine prostatic adenocarcinoma (AC) and compare with human disease

Study Design – Retrospective

Materials and Methods:

- 20 cases collected at necropsy (11 neutered, 9 intact), selected based on clinical signs
- Histopathology and histochemistry (acid phosphatase, oil red O, PAS, Sudan Black).

Conclusions drawn:

- Prostatic carcinoma often resembles the human counterpart morphologically and pathologically, although being rare.

- ACs are classified in two different subtypes: type A (intraalveolar, small acinar), type B (syncytial type, discrete epithelial type).
- Hormonal imbalances may play an important role in the pathogenesis of both canine and human prostate ACs.

Statistical soundness – None performed

SUBGROUP CONCLUSIONS: This is a historical observational study that paved the way for further comparison. Although providing a detailed histologic description of this tumor, major findings are now considered “textbook” including advanced age at presentation, overall frequency, pattern of metastasis, and morphologic similarities to human prostate cancer (hPC). Modern techniques (especially clinical imaging and IHC), larger sample size and changes in veterinary practices (especially castration), make some of the data obsolete.

2. Cornell KK, Bostwick DG, Cooley DM, Hall G, Harvey HJ, Hendrick MJ, Pauli BU, Render JA, Stoica G, Swett DC, Waters DJ. Clinical and Pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases. Prostate 2000; 45: 173-183.

Study Objective – Document the clinical, gross and microscopic findings of spontaneous prostate carcinoma. The authors sought to examine whether factors such as age at prostate cancer diagnosis or lifetime exposure to testicular hormones might influence the morphology or metastatic behavior of these tumors.

Study Design – Retrospective

Materials and Methods:

- Case selection based on database mining from 6 veterinary teaching hospitals
- Criteria for inclusion: histopathologic diagnosis of PC, postmortem evaluation, availability of tissue blocks for histopathologic review, sufficient medical record data.
- 76 cases examined.
- Tumors classified as adenocarcinoma, urothelial carcinoma, squamous cell carcinoma, mixed morphology.
- The analyzed data included age, castration status, body weight, metastatic frequency and metastatic location.

Conclusions drawn – This study provides more complete characterization of PC in terms of morphologic heterogeneity, skeletal metastases, and influence of testicular hormones than previous reports. Adenocarcinoma and mixed morphology were observed in 90% of cases. Intact dogs were more likely to develop adenocarcinoma.

Statistical soundness – Solid, although not all the correlations were statistically analyzed.

SUBGROUP CONCLUSIONS: This study includes a relevant number of cases and represents a good attempt at classifying prostate cancer, although the histologic description of the different growth patterns is too superficial. Good attempt to align

features with clinical outcome. There appears to be a trend for increased rate of skeletal metastases in dogs castrated at a young age, but it was not statistically significant. Details on the differentiation between prostatic adenocarcinoma and urothelial carcinoma are lacking, as well as any immunohistochemical characterization (e.g. CK7, UPIII) to confirm if all cancers were arising from the prostate gland or the urothelium of ducts or urethra.

3. LeRoy BE, Nadella MVP, Toribio RE, Leav I, Rosol TJ (2004). Canine prostate carcinomas express markers of urothelial and prostatic differentiation. Vet Pathol, 41: 131-140.

Study Objective – To investigate the origin of canine prostatic neoplasms, the authors analyzed CK7 and arginine esterase (AE) expression in normal canine prostate and urothelium and compared their findings with malignancies arising in these tissues.

Study Design – retrospective.

Materials and Methods:

- 51 tissue blocks (normal and neoplastic canine bladder and prostate) from 3 different institutions for CK7 immunohistochemistry;
- 12 tissue samples (5 normal prostate, 3 normal bladders, 2 TCCs, 4 prostate carcinomas) tested by RT-PCR for AE.

Conclusions drawn:

- Light microscopy was not able to separate urothelial from glandular types;
- CK7 expression suggested ductal origin or common origin of urothelium and prostate (dedifferentiation);
- AE is present in urothelium and prostatic tissue, as well as in neoplastic tissue.

Statistical soundness – no statistics performed.

SUBGROUP CONCLUSIONS: This represents the first paper on canine prostate cancer focusing on the issue of differential diagnoses and investigating the cell-of-origin. The introduction for this manuscript is excellent in defining the issues surrounding the difficulty in differentiating between prostatic AC and TCC. The heterogeneous histopathologic appearance of PC in dogs, coupled with the lack of a prostate-specific immunohistochemical marker suitable for canine tissues, led the authors to the conclusion that accurate classification of PC was not always possible with traditional light microscopic evaluation. Unfortunately, CK7 could not discriminate between transitional cell and PC (expressed in a similar manner). Despite being published in 2004, the authors still use the original classification proposed by Leav and Ling in 1968.

4. Lai CL, van den Ham R, van Leenders G, van der Lugt J, Mol JA, Teske E. Histopathological and immunohistochemical characterization of canine prostate cancer. Prostate, 2008, 68(5): 477-488.

Study Objective – To identify the cell of origin by histopathologic classification into subtypes and comparing these with immunohistochemical detection of cytokeratins

(HMWCK, CK14, CK5, CK18, CK7), UPIII, prostate specific antigen (PSA), and prostate specific membrane antigen (PSMA).

Study Design – retrospective.

Materials and Methods:

- FFPE specimens from 20 dogs (11 neutered, 9 intact) from the archives of Utrecht University
- IHC analysis.

Conclusions drawn – Canine PC appears to be more aggressive and of a less differentiated type than most human PC. Based on CK7 and UPIII staining, canine PC most likely originates from the collecting ducts rather than peripheral acini.

Statistical soundness – Chi square not appropriate for multiple comparisons between groups.

SUBGROUP CONCLUSIONS: The various classifications of canine PC of previous studies are listed and further subtypes are defined (micropapillary, cribriform, solid, sarcomatoid, small acinar/ductal, tubulopapillary). However, this study is too small to draw many conclusions about the population of cPC patients and their tumors as a whole and there is no clear definition of what is an urothelial carcinoma of the canine prostate. A high proportion of cases were positive for CK7 (17/20) and 12 of these 17 were also UPIII positive. Since CK7 and UPIII are commonly expressed in epithelium of the urethra, it calls into question the cellular origin of the cPC that were studied. In addition, it is not clear that the PSA antibody binds to any relevant antigen, especially since dogs do not have a highly homologous gene to PSA. The PSMA work is very hard to interpret as the data is just summarized and no stats were conducted.

5. Palmieri C, Lean FZ, Akter SH, Romussi S, Grieco V. A retrospective analysis of 111 canine prostatic samples: histopathological findings and classification. Res Vet Sci, 2014; 97: 568-573.

Study Objective – The goals of this study were (a) to present the diagnostic histopathologic features to the different conditions commonly or uncommonly observed in the canine prostate; (b) to evaluate the real frequency of preneoplastic lesions, and (c) to describe the histologic variants of canine PC in order to provide a comprehensive and consistent presentation of the different subtypes.

Study Design – retrospective

Materials and Methods:

- FFPE specimens from 111 dogs collected from the archives of 2 universities
- Histopathology (classification as benign prostatic hyperplasia - BPH, squamous metaplasia, prostatitis, high grade prostatic intraepithelial neoplasia - HGPIN, proliferative inflammatory atrophy - PIA, PC).
- Neuter status not known.

Conclusions drawn – Canine PC showed considerable morphologic heterogeneity. Different subtypes of carcinoma were categorized, with the main subtypes as follows: small acinar/ductal, solid, cribriform and papillary. Other types were

recognized – sarcomatoid, mucinous, squamous – with the mixed types less common than other papers.

Statistical soundness – None performed.

SUBGROUP CONCLUSIONS: A comprehensive description of the morphologic and histologic features of PC can be found in this manuscript, which also emphasized previously reported findings regarding substantial heterogeneity in cPC morphology. However, the complete lack of information on castration status makes comparisons to other studies difficult. In addition, there are no details on the differentiation between prostatic adenocarcinoma and urothelial carcinoma, as well as any immunohistochemical characterization (e.g. CK7, UPIII) to confirm if all cancers were arising from the prostate gland or the urothelium of ducts or urethra.

6. Akter SH, Lean FZ, Lu J, Grieco V, Palmieri C. Different growth patterns of canine prostatic carcinoma suggests different models of tumor-initiating cells. Vet Path 2015,52(6), 1027-1033.

Study Objective – To identify the cell of origin of prostate carcinoma through the expression of different markers (CK8/18, CK5, CK14, AR).

Study Design – retrospective

Materials and Methods:

- Seventy-seven FFPE samples (8 normal, 35 BPH, 34 PC) from archives
- IHC for selected markers.

Conclusions drawn – Predominance of AR, CK8/18 positivity indicate differentiated phenotypes in carcinomas, with the most prevalent histopathologic subtype being cribriform and solid. Intermediate cell types were assumed based on some CK5 and CK14 staining. Much of the study is descriptive so the data like the frequency of various histopathologic patterns and IHC immunolabelling are sound.

Statistical soundness – Comparisons were between number of cells stained between different types of carcinomas.

SUBGROUP CONCLUSIONS: The introduction is well-written and provides a thorough comparison of the relationships between PC in humans and dogs. However, different selection criteria, targets and controls make comparison with previous literature difficult. The unknown castration status of the dogs makes some interpretation difficult, especially the degree of AR positivity in control tissues. The use of AR positivity to rule out urothelial origin of cPC is not supported by data or the findings of the cited paper.

APPENDIX

Classification of prostatic carcinoma

WHO International Histopathologic Classification of Tumors of Domestic Animals (1998)	<i>WHO classification of tumors, of the urinary system and male genital organs (2016)</i>	Lai et al. (2007), Palmieri et al. (2014)
<ul style="list-style-type: none"> • Adenocarcinoma: <ul style="list-style-type: none"> – Alveolar – Acinar • Poorly differentiated carcinoma 	<ul style="list-style-type: none"> • Acinar adenocarcinoma: <ul style="list-style-type: none"> – Atrophic – Pseudohyperplastic – Microcystic – Foamy gland – Mucinous – Signet ring-like cell – Pleomorphic giant cell – Sarcomatoid • Ductal adenocarcinoma: <ul style="list-style-type: none"> – Cribriform – Papillary – Solid • Intraductal carcinoma • Urothelial carcinoma • Squamous neoplasms: <ul style="list-style-type: none"> – Adenosquamous carcinoma – Squamous cell carcinoma • Basal cell carcinoma 	<ul style="list-style-type: none"> • Papillary • Cribriform (with and without comedonecrosis) • Solid • Small acinar/ductal • Signet ring • Mucinous • Sarcomatoid

References:

1. Lai CL, van den Ham R, van Leenders G, van der Lugt J, Mol JA, Teske E. *Histopathological and immunohistochemical characterization of canine prostate cancer*. Prostate, 2008, 68(5): 477-488.
2. Palmieri C, Lean FZ, Akter SH, Romussi S, Grieco V. *A retrospective analysis of 111 canine prostatic samples: histopathological findings and classification*. Res Vet Sci, 2014; 97: 568-573.
3. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO classification of tumours, of the urinary system and male genital organs*. Fourth edition. IARC, 2016.
4. Kennedy PC, Cullen JM, Edwards JF, Goldschmidt MH, Larsen S, Munson L, et al. 1998. *Histological Classification of Tumors of the Genital System of Domestic Animals*. WHO International Histological Classification of Tumors of Domestic Animals, second series. Vol. 4. American Registry of Pathology, AFIP: Washington DC, pp.21-22.