

**VCS/ACVP Oncology-Pathology Working Group
Canine Mammary Tumor Subgroup
Consensus on the Classification and Grading
of Canine Mammary Tumors**

Species/Tumor: Canine Mammary Tumor Subgroup

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OVERALL SUMMARY / RECOMMENDATIONS:

The *Canine Mammary Tumor Subgroup* has concluded and recommends the following regarding *classification and grading for canine mammary tumors*.

Based on critical review of the selected literature (listed below) the members of the OPWG Canine Mammary Tumor Subgroup recommend the histological classification of Goldschmidt et al [1] and the grading system established by Peña et al [3], which employed the Goldschmidt classification system in its study design.

Consensus on Histological classification

The histological classification recommended by the group is the one proposed by Goldschmidt et al., 2011[1] (Annex 1).

There is currently not enough information to prognosticate all tumor subtypes by histological classification alone. Some studies have established an association between prognosis and some, but not all, of the histological subtypes [2, 3]. Rasotto et al. [2] found in a retrospective study including cases with submitted lymph node for histopathological analysis that the tumor types with high incidence of lymphatic invasion at diagnosis were anaplastic carcinoma (100%), invasive micropapillary carcinoma (100%), adenosquamous carcinoma (100%), lipid-rich carcinoma (100%), comedocarcinoma (94.0%), solid carcinoma (87.1%), and simple tubulopapillary carcinoma (82.1%). The tumors with low incidence of lymphatic invasion were complex carcinoma (20%), carcinoma arising in benign mixed tumor (20%) and ductal carcinoma (14.3%). In a prospective study by Peña et al. [3], tumors were divided into three histological groups according to prognoses reported in previous studies. Those in group 2 (solid carcinoma, comedocarcinoma, carcinoma, malignant myoepithelioma and anaplastic carcinoma) had a worse prognosis than those in group 1 (in situ carcinoma, simple carcinoma, carcinoma arising in a mixed tumor, complex carcinoma, mixed-type carcinoma, ductal carcinoma, and adenosquamous carcinoma). Group 3 comprised tumor types that were represented too infrequently; therefore, Group 3 diagnoses (anaplastic carcinoma, squamous cell carcinoma, lipid rich carcinoma, malignant myoepithelioma and carcinosarcoma) could not be statistically assessed for prognosis.

The histological classification provides an effective and concise means of communication between pathologists, oncologists, clinicians and researchers. The association between the various histological types / classifications and prognosis has not yet been established for some of the more rare subtypes and will require large, prospective and well-designed studies comprised of multiple institutions globally. Nevertheless, according to many previous studies, solid tumors have worse prognosis than tubular or papillary tumors [4-6].

Proposed Histologic Classification: 2010**1: Malignant Epithelial Neoplasms**

Carcinoma—in situ
 Carcinoma—simple
 a. Tubular
 b. Tubulopapillary
 c. Cystic-papillary
 d. Cribriform
 Carcinoma—micropapillary invasive
 Carcinoma—solid
 Comedocarcinoma
 Carcinoma—anaplastic
 Carcinoma arising in a complex adenoma/mixed tumor
 —The benign counterpart is still detectable in the section.
 Carcinoma—complex type
 —The epithelial component is malignant, and the myoepithelium is benign.
 Carcinoma and malignant myoepithelioma
 —The epithelial and myoepithelial components are malignant.
 Carcinoma—mixed type
 —The epithelial component is malignant; the myoepithelial mesenchymal component is benign; and the mesenchymal component is cartilage or bone.
 Ductal carcinoma—malignant counterpart of ductal adenoma
 Intraductal papillary carcinoma—malignant counterpart of intraductal papillary adenoma

2: Malignant Epithelial Neoplasms—Special Types

Squamous cell carcinoma
 Adenosquamous carcinoma
 Mucinous carcinoma
 Lipid-rich (secretory) carcinoma
 Spindle cell carcinomas
 Malignant myoepithelioma
 Squamous cell carcinoma—spindle cell variant
 Carcinoma—spindle cell variant
 Inflammatory carcinoma (see Inflammatory Carcinoma section)

3: Malignant Mesenchymal Neoplasms—Sarcomas

Osteosarcoma
 Chondrosarcoma
 Fibrosarcoma
 Hemangiosarcoma
 Other sarcomas

4: Carcinosarcoma—Malignant Mixed Mammary Tumor**5: Benign Neoplasms**

Adenoma—simple
 Intraductal papillary adenoma (duct papilloma⁹)
 Ductal adenoma (basaloid adenoma⁹)

With squamous differentiation (keratohyaline granules)
 Fibroadenoma
 Myoepithelioma
 Complex adenoma (adenomyoepithelioma)
 Benign mixed tumor

6: Hyperplasia/Dysplasia

Duct ectasia
 Lobular hyperplasia (adenosis)
 Regular
 With secretory activity (lactational)
 With fibrosis—interlobular fibrous connective tissue
 With atypia
 Epitheliosis
 Papillomatosis
 Fibroadenomatous change
 Gynecomastia

7: Neoplasms of the Nipple

Adenoma
 Carcinoma
 Carcinoma with epidermal infiltration (Paget-like disease)

8: Hyperplasia/Dysplasia of the Nipple

Melanosis of the skin of the nipple

Criteria of Malignancy

A major problem in evaluating canine mammary neoplasms is identifying those neoplasms that are “truly” malignant. The presence of some cells, with enlarged nuclei and prominent nucleoli, often leads to the overdiagnosis of mammary carcinoma. The following are the most significant criteria for the diagnosis of malignant mammary tumors in the dog based on hematoxylin and eosin–stained sections:

- tumor type,
- significant nuclear and cellular pleomorphism,
- mitotic index,
- presence of randomly distributed areas of necrosis within the neoplasm,
- peritumoral and lymphatic invasion, and
- regional lymph node metastasis.

Tables 2 and 3 elaborate on some of these features.

Consensus on Grading

The grading system recommended by the group is the one proposed by Pena et al., 2013[3] (Table 1).

The histological grade is indeed an important independent prognostic indicator in dogs with mammary carcinoma. The Peña system is the only grading system that has been validated in dogs in a prospective study [3]. In this study, 65 female dogs with at least one malignant tumor were recruited, clinically evaluated, surgically treated, and followed up (minimum follow-up 28 months, maximum 38 months). It includes explanations on how to assess the grade of tumors with myoepithelial proliferation. Sarcomas and carcinosarcomas cannot be graded using this system. The usefulness of this system for some rare tumors remains to be validated in a larger series of cases containing these specific types (i.e. cribiform carcinoma, micropapillary carcinoma, mucinous carcinoma, carcinoma and malignant myoepithelioma, and spindle cell carcinomas). The grading system is fully explained in the table below as it was originally published³.

Table 1. Histological Grading System for Canine Mammary Cancer.

Criteria for Histological Malignancy Grade		
A. Tubule Formation ^a	Points	
	1	Formation of tubules in >75%
	2	Formation of tubules in 10%–75% (moderate formation of tubular arrangements admixed with areas of solid growth)
B. Nuclear Pleomorphism ^b	3	Formation of tubules in (<10%) (minimal or no tubule formation)
	1	Uniform or regular small nucleus and occasional nucleoli
	2	Moderate degree of variation in nuclear size and shape, hyperchromatic nucleus, presence of nucleoli (some of which can be prominent)
C. Mitoses per 10 HPF ^c	3	Marked variation in nuclear size, hyperchromatic nucleus, often with ≥ 1 prominent nucleoli
	1	0–9 mitoses/10 HPF
	2	10–19 mitoses/10 HPF
Histological Malignancy Grade Total Scoring (A + B + C)	3	≥20 mitoses/10 HPF
	Points	Grade of Malignancy
	3–5	I (low, well differentiated)
	6–7	II (intermediate, moderately differentiated)
	8–9	III (high, poorly differentiated)

^a In complex and mixed tumors, the percentage of tubular formation is scored considering only epithelial areas. In malignant myoepithelioma, tubular formation is 2. In heterogeneous canine mammary carcinomas, tubular scoring should be assessed in the most representative malignant area.

^b In complex and mixed tumors, nuclear pleomorphism is evaluated in all the malignant components.

^c HPF, high-power field. The fields are selected at the periphery or the most mitotically active parts of the sample (not only epithelial cells). Diameter of the field of view = 0.55 mm.

ADDITIONAL AREAS OF DISCUSSION AMONGST SUBGROUP MEMBERS:

1. Histological description

In general, the subgroup feels a good histological description should include, but not be limited to, all the characteristics listed below (if present in the section examined):

- Absence/presence of myoepithelial proliferation
- Vascular invasion
- Tumor infiltration
- Necrosis
- Mitotic index: low (0-9), medium (>9-19), high (>19) (per 10 HPF, in the most mitotically active areas) (used also for grading, diameter of the field of view 0.55mm)
- The presence of any type of desmoplasia, especially at the periphery of the tumor

Absence of myoepithelial proliferation [7-9], vascular invasion [10-11] and necrosis [10] have been associated with a worse prognosis in several retrospective and prospective studies. The peripheral tumor infiltration is a significant factor in predicting the likely risk of invasion of the lymphatic system and it has been associated with stromal desmoplasia. Therefore, when a diagnosis of mammary carcinoma is made, the tissue surrounding the tumor should be evaluated, and when areas of stromal desmoplastic reaction are found, a careful search for entrapped neoplastic cells should be undertaken [2].

2. Margins

Regarding tissue margins, the subgroup suggests:

Not only should tumor-free margin measurements be reported, but the presence of any possible preneoplastic or premalignant changes in the surrounding mammary tissue should be mentioned [12].

FUTURE DIRECTIONS / RECOMMENDED STUDIES:

1. Molecular classification

In the last years, several attempts have been made to apply the human classification system of breast cancer to canine mammary tumors. According to the expression of different markers (e.g. hormonal receptors, HER-2, basal markers) the classical molecular classification divides breast tumors into luminal A, luminal B, basal type, Her-2 overexpression and normal type. The application of the molecular classification in CMTs is still uncertain but promising (e.g. [13]). It would be ideal to have this molecular subtyping in the future with information obtained from prospective studies indicating if there is a prognostic or predictive (therapeutic) relevance. Additional studies should be recommended in a systematic way.

Molecular subtyping can be performed using different antibody panels on formalin fixed tissue and/or expression analyses directly detecting RNA-expression.

2. Multicentric Prospective Studies

This consensus document recommends that future multicentric studies should employ, as a minimum, the histological classification system of Goldschmidt et al (2011) [13] and the grading system of Pena et al (2013) [3]. Nevertheless, the group encourages additional future multicentric prospective studies that include representative number of cases with infrequent diagnoses and which would serve to confirm and lend further validation to the findings by Pena et al [3].

FUTURE GOALS OF THE OPWG CMT SUBGROUP:

In Phase 2, the Canine Mammary Tumor group intends to address the literature and achieve consensus on the subjects below:

1. Cytology of CMTs

Due to their histological heterogeneity, cytologic diagnosis of canine mammary tumors is less accurate than for other tumor types, with lower sensitivity and specificity [14-17]. In one study, the cytologic diagnosis was accurate and associated with the survival [18].

Future discussion on this topic is needed, although fine needle aspiration for cytologic examination is not currently recommended for canine mammary tumors on a standard basis.

2. Prognostic factors

2.1. Clinical prognostic factors

- TNM staging
- Ovariectomy at time of surgery

2.2. Histopathological prognostic factors (other than grading)

2.3. Immunohistochemical prognostic factors

- Proliferation markers
- Hormonal receptors
- Markers for molecular classification

3. Updates

- This consensus document should aim to be updated as new relevant publications are released. The interval has to be further discussed and be part of a continuous task for OPWG as for any consensus document produced.

References

1. Goldschmidt, M., et al., *Classification and grading of canine mammary tumors*. Vet Pathol, 2011. **48**(1): p. 117-31.
2. Rasotto, R., et al., *A retrospective study of those histopathologic parameters predictive of invasion of the lymphatic system by canine mammary carcinomas*. Vet Pathol, 2012. **49**(2): p. 330-40.
3. Pena, L., et al., *Prognostic value of histological grading in noninflammatory canine mammary carcinomas in a prospective study with two-year follow-up: relationship with clinical and histological characteristics*. Vet Pathol, 2013. **50**(1): p. 94-105.
4. Philibert, J.C., et al., *Influence of host factors on survival in dogs with malignant mammary gland tumors*. J Vet Intern Med, 2003. **17**(1): p. 102-6.
5. Shofer, F.S., et al., *Histopathologic and dietary prognostic factors for canine mammary carcinoma*. Breast Cancer Res Treat, 1989. **13**(1): p. 49-60.
6. Yamagami, T., et al., *Prognosis for canine malignant mammary tumors based on TNM and histologic classification*. J Vet Med Sci, 1996. **58**(11): p. 1079-83.
7. Yamagami, T., et al., *Prognosis for canine malignant mammary tumors based on TNM and histologic classification*. Journal of Veterinary Medical Science, 1996. **58**(11): p. 1079-1083.
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9. Pena, L., et al., *Prognostic Value of Histological Grading in Noninflammatory Canine Mammary Carcinomas in a Prospective Study With Two-Year Follow-Up: Relationship With Clinical and Histological Characteristics*. Vet Pathol, 2012.
10. de Las Mulas, J.M., Y. Millan, and R. Dios, *A prospective analysis of immunohistochemically determined estrogen receptor alpha and progesterone receptor expression and host and tumor factors as predictors of disease-free period in mammary tumors of the dog*. Vet Pathol, 2005. **42**(2): p. 200-12.
11. Sassi, F., et al., *Molecular-based tumour subtypes of canine mammary carcinomas assessed by immunohistochemistry*. BMC Vet Res, 2010. **6**: p. 5.
12. Mouser, P., et al., *Prevalence and classification of spontaneous mammary intraepithelial lesions in dogs without clinical mammary disease*. Vet Pathol, 2010. **47**(2): p. 275-84.
13. Im, K.S., et al., *Analysis of a new histological and molecular-based classification of canine mammary neoplasia*. Vet Pathol, 2014. **51**(3): p. 549-59.
14. Griffiths, G.L., J.H. Lumsden, and V.E. Valli, *Fine needle aspiration cytology and histologic correlation in canine tumors*. Vet Clin Pathol, 1984. **13**(1): p. 13-7.
15. Allen, S.W., K.W. Prasse, and E.A. Mahaffey, *Cytologic differentiation of benign from malignant canine mammary tumors*. Vet Pathol, 1986. **23**(6): p. 649-55.
16. Hellmen, E. and A. Lindgren, *The accuracy of cytology in diagnosis and DNA analysis of canine mammary tumours*. J Comp Pathol, 1989. **101**(4): p. 443-50.

17. Stockhaus, C. and E. Teske, *[Clinical experiences with cytology in the dog]*. Schweiz Arch Tierheilkd, 2001. **143**(5): p. 233-40.
18. Simon, D., et al., *Cytologic examination of fine-needle aspirates from mammary gland tumors in the dog: diagnostic accuracy with comparison to histopathology and association with postoperative outcome*. Vet Clin Pathol, 2009. **38**(4): p. 521-8.

LITERATURE REVIEWED:

All literature listed below was critically reviewed by the subgroup and formed the basis from which the consensus was generated

1. Vet Pathol. 2013 Sep 3.

Analysis of a New Histological and Molecular-Based Classification of Canine Mammary Neoplasia. Im KS, Kim NH, Lim HY, Kim HW, Shin JI, Sur JH.

Study Objective: Retrospective analysis of a continuous series of Korean CMTs to classify according to Goldschmidt et al and also nested retrospective analysis of 159 randomly selected carcinomas from that cohort according to an immunohistochemical classification scheme derived from human mammary tumor management.

Study Design (e.g. retrospective, prospective, other): retrospective

Materials & Methods: 648 archived mammary tumor specimens. Of which 159/340 carcinomas were randomly selected for immunohistochemical classification

Conclusions Drawn: The authors make statements about the associations between histological type and molecular subtype and between histological grade and molecular subtype.

Statistical Soundness: It is a large study and hence it should be possible to use good models on it. The Group not satisfied with models used.

SUBGROUP CONCLUSIONS: Efforts of molecular classification. The Group however think that this paper does not provide meaningful clinical data to combine this with – namely prognosis and treatment outcome. The Group lacks data on cytokeratin.

2. Cancer Cell Int. 2013 Aug 9;13(1):79.

Diagnosis, classification and grading of canine mammary tumours as a model to study human breast cancer: a Clinico-Cytohistopathological study with environmental factors influencing public health and medicine. Shafiee R,

Javanbakht J, Atyabi N, Kheradmand P, Kheradmand D, Bahrami A, Daraei H, Khadivar F.

Study Objective: To identify cytopathological criteria for malignancy in CMTs, the define the frequency of different histopathological tumor types and the relationship between histological type and histological grade and to apply a human grading scheme to attempt to discriminate simple from complex and mixed tumour types.

Study Design (e.g. retrospective, prospective, other): Prospective

Materials & Methods: 15 cases with mammary masses that underwent cytology and histology evaluations

Conclusions Drawn: Cytology can reliably classify tumor types and will have a bearing on all future mammary tumor studies

Statistical Soundness: None

SUBGROUP CONCLUSIONS: This is an irrelevant paper, which should not be considered or mentioned in the consensus document. The number of dogs is too low, the objectives are confusing, clinical data are not included.

3. Vet Pathol. 2013 Jan; 50(1):94-105.

Prognostic value of histological grading in noninflammatory canine mammary carcinomas in a prospective study with two-year follow-up: relationship with clinical and histological characteristics. Peña L, De Andrés PJ, Clemente M, Cuesta P, Pérez-Alenza MD.

Study Objective: Evaluation of Prognostic Impact of Goldschmidt histological classification of mammary carcinomas and Pena histological grade scheme.

Study Design (e.g. retrospective, prospective, other): Prospective

Materials & Methods: 65 consecutive mammary carcinoma cases, treated uniformly and followed up for 28-38 months

Conclusions Drawn: Histological grade and clinical stage (WHO stage and proposed new T stage <1cm vs 1-3cm) are of prognostic significance. Carcinomas types which are sufficiently numerous to be tested also shown to be prognostically significant.

Statistical Soundness: Excellent

SUBGROUP CONCLUSIONS: The Pena grading scheme is of true prognostic importance and is suggested to be used onwards in larger studies. Some

concern is raised by group members that it may still be a bit too detailed or “academic” to be adopted by the general pathology community and understood by the clinicians. Information on margins is missing in this paper. Surgical margins should also be reported on the pathology report. As stated in the Pena study, mammary carcinoma size should be recorded in centimeter units in future prognostic studies.

4. Vet Pathol. 2012 Mar;49(2):330-40.

A retrospective study of those histopathologic parameters predictive of invasion of the lymphatic system by canine mammary carcinomas. Rasotto R, Zappulli V, Castagnaro M, Goldschmidt MH

Study Objective: To identify histological characteristics that can predict outcome using lymphatic vessel invasion and regional lymph node metastases as proxy markers of prognosis

Study Design (e.g. retrospective, prospective, other): Retrospective

Materials & Methods: 245 archived CMT specimens with lymph node sample. No follow-up study.

Conclusions Drawn: Histological classification, histological grade (Peña Clemente/ >Misdorp), micropapillary pattern and local tumor infiltration were the statistically significant parameters which, combined, gave the most accurate prediction of regional lymph node metastasis and/or lymphatic vessel invasion. Presence or absence of vasculogenic mimicry did not achieve significance.

Statistical Soundness: Good

SUBGROUP CONCLUSIONS: Peña/Clemente grading system is more accurate than the Misdorp system. Study supports the value of the Goldschmidt classification in analyze peripheral infiltration, micropapillary pattern and tumor grade. Statistical mistake regarding vasculogenic mimicry (it is significant at univariate level). Grade is not perfect; there are histological classifications which carry a higher risk of metastasis than others.

5. Vet Pathol. 2011 Jan;48(1):117-31.

Classification and grading of canine mammary tumors. Goldschmidt M, Peña L, Rasotto R, Zappulli V

Study Objective: To present the evolution of canine mammary tumor classification and an updated scheme which incorporates more recently identified morphological

subtypes of CMT. By providing a definitive resource that more accurately discriminates morphologically distinct CMT subtypes, it is hoped that more accurate prognostic judgments can be made.

Study Design (e.g. retrospective, prospective, other): Literature review/Expert Opinion

Materials & Methods: NA

Conclusions Drawn: NA

Statistical Soundness: NA

SUBGROUP CONCLUSIONS: Studies of canine mammary carcinomas that have since used this classification system in conjunction with a grading system have already shown the validity of its use for prognostication. We too will recommend it for any future study of aspects that may predict the clinical outcome. Members of the Group again raised concerns that there is a risk of having too complicated grading systems, too detailed and hence mostly disapproved by clinicians. The paper gives a good overview on the current state of the art in the classification and grading.

6. Braz J Vet Pathol. 2011, 4:153–180.

Consensus for the diagnosis, prognosis and treatment of canine mammary tumors. Cassali GD, Lavalle GE, De Nardi AB, et al.

Study Objective: To present a consensus of expert Brazilian opinion regarding the diagnosis and management of canine mammary tumors.

Study Design (e.g. retrospective, prospective, other): Expert opinion

Materials & Methods: Literature review/expert opinion

Conclusions Drawn: We need to use knowledge of histological type and grade to better characterize CMTs. There are immunohistochemical evaluations which can allow us to stratify cases according to other prognostic markers, eg MIB-1, COX-2.

Statistical Soundness: NA

SUBGROUP CONCLUSIONS: Up to now, the classification here proposed has not been applied and validated in any peer-reviewed article. The classification system suggested is a bit more complex through the inclusion of some more categories), making it potentially more difficult to be applied with consistency. The grading system that these authors suggest is very similar

(except for minor differences in the mitotic cut-offs) to the system validated by Karayannopoulou (reference 9).

7. BMC Vet Res. 2010 Jan 28;6:5.

Molecular-based tumour subtypes of canine mammary carcinomas assessed by immunohistochemistry. Sassi F, Benazzi C, Castellani G, Sarli G.

Study Objective: To assess whether application of an immunohistochemistry based carcinoma classification scheme derived from mRNA profile based classification of mammary carcinoma in humans would bear any relation to other known prognostic indicators: invasion and grade, or would be a prognostic variable in its own right.

Study Design (e.g. retrospective, prospective, other): Prospective

Materials & Methods: 45 dogs presented to a number of clinics with primary mammary tumors and followed-up after mammary mass resection

Conclusions Drawn: The 'molecular characterization' did not show an independent association with survival.

Statistical Soundness: Since all tumors are considered equally under the investigators' terms of assessment, 45 is an acceptable number for the statistical analyses performed.

SUBGROUP CONCLUSIONS: Molecular subtypes using human-IHC surrogates is appealing and promising, but at this stage there are no enough data to justify its application in the routine diagnostic. Invasion and grade again revealed to be highly relevant for prognosis in dogs with canine mammary tumors.

8. Vet Comp Oncol. 2009 Sep;7(3):162-72

Canine mammary gland tumours; a histological continuum from benign to malignant; clinical and histopathological evidence. K. U. Sorenmo, V.M. Kristiansen, M. A. Cofone, F. S. Shofer, A.-M. Breen, M. Langeland, C.M.Mongil, A.M. Grondahl, J. Teige and M. H. Goldschmidt.

Study Objective: To determine whether simple clinical or histological characteristics could provide prognostic information in CMTs. Prognosis is principally judged by the designation of benign or malignant tumour.

Study Design (e.g. retrospective, prospective, other): Prospective

Materials & Methods: Patients presented for management of spontaneous mammary tumors.

Conclusions Drawn: Size is a strong indicator of malignancy. 'Ownership' of a single malignant tumor greatly increases the risk of a second one.

Statistical Soundness: Good.

SUBGROUP CONCLUSIONS: Progression from benign to malignant lesions is possible, especially for some specific tumor subtypes (e.g. from benign mixed tumor to carcinoma in benign mixed tumor) and this needs to be taken into consideration when dogs present with small (likely benign) mammary lumps. This study validates the suggestion that tumors are categorized further according to primary tumor size than is currently recommended by the WHO clinical stage scheme.

9. J Comp Pathol. 2005 Nov;133(4):246-52.

Histological grading and prognosis in dogs with mammary carcinomas: application of a human grading method. Karayannopoulou M, Kaldrymidou E, Constantinidis TC, Dessiris A.

Study Objective: To test the usefulness of the Elston and Ellis grading method in a number of canine mammary carcinoma cases

Study Design (e.g. retrospective, prospective, other): Prospective

Materials & Methods: 85 cases with spontaneously occurring malignant mammary tumors including malignant tumors which had arisen in a benign lesion but which predominated

Conclusions Drawn: Grading according to Elston and Ellis is of prognostic significance. The precise impact of grade varies with some histological types.

Statistical Soundness: Good

SUBGROUP CONCLUSIONS: This is a well-performed and robust study. It does justify use of the Elston and Ellis method to a certain degree. The study provides the information regarding the field diameter used for the mitotic count. This important aspect is often neglected by authors and reviewers of prognostic studies and is something we should recommend. This paper concludes that a reproducible grading scheme is more useful than knowing the histologic subtype when it comes to prognosis.

10. J Vet Med Sci. 1996 Nov;58(11):1079-83.

Prognosis for canine malignant mammary tumors based on TNM and histologic classification. Yamagami T, Kobayashi T, Takahashi K, Sugiyama M.

Study Objective: Evaluate prognostic impact of tumour stage and other histological parameters

Study Design (e.g. retrospective, prospective, other): Retrospective

Materials & Methods: Archived tumor specimens and case records for dogs with mammary tumors in the Tokyo region

Conclusions Drawn: Clinical stage was of great prognostic significance. Other significant factors included histological type (broad categories), myoepithelial cell proliferation, local tumor infiltration, vascular invasion

Statistical Soundness: No multivariable analyses were performed.

SUBGROUP CONCLUSIONS: The TNM classification is useful in prognostication of canine mammary tumors. Intravascular invasion is associated with a poorer prognosis. The malignant histologic classification is also useful in prognostication, with non-tubular carcinomas having a poorer prognosis. Much all its observations confirmed through more recent studies using standardized methods.

LITERATURE CITED AND ADDRESSED IN SUBGROUP DISCUSSIONS BUT NOT OFFICIALLY REVIEWED:

Allen SW, Prasse KW, Mahaffey EA. Cytologic differentiation of benign from malignant canine mammary tumors. *Vet Pathol.* 1986;23:649-655

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Stockhaus C, Teske E. Clinical experiences with cytology in the dog. Schweiz Arch Tierheilkd. 2001;143:233-240