The Pharma Innovation Journal 2019; 8(4): 149-151

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(4): 149-151

www.thepharmajournal.com
Received: 11-02-2019
Accepted: 15-03-2019

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# Canine mammary tumours: Histological malignancy grading as a prognostic indicatior

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**Abstract**
Histopathology is considered as the gold standard for diagnosis of canine mammary tumours (CMTs). Like human breast cancer, mammary tumour is a common tumour in dogs. Mastectomy is the most commonly adopted approach for treatment of CMTs. Grading of the tumour by histopathology is an effective tool to assess its biological behaviour and aggressiveness. In humans, Elston and Ellis grading method is routinely used to grade breast carcinomas. Present study was aimed at classification and histological malignancy grading of CMTs that were reported in and around Thrissur, Kerala, by using the modified human grading method. The samples included 16 tumours of canine mammary gland. Out of these, 87.5% (n=14) were malignant and 12.5% (n=2) were benign. After grading, it was found that 21.4% (n = 3) of the malignant tumours were of grade I, 57.1% (n = 8) were grade II and 21.4% (n= 3) were grade III tumours. The study revealed that majority of the simple carcinomas (most malignant type) were grade III or II and all the grade III tumours recurred within six months. Hence grading of the tumours was an effective prognostic indicator for planning further line of treatment. This study is first of its kind to classify and grade CMTs common in this area.

**Keywords:** Canine, histopathology, grading, mammary Tumour

## 1. Introduction
Mammary tumour is the second most common tumours encountered in dogs after skin tumours, and is the most common type of tumour seen in female dogs. Around 20-80% of the canine mammary tumours are found to be malignant [9]. Accurate histopathological diagnosis plays a crucial role in predicting the biological behaviour, assessing the prognosis and deciding the further course of treatment [7]. Grading of a tumour is the process of identifying those characteristics of the mammary tumour that determine the malignancy and prognosis, which can be intimated to the treating veterinarian and accordingly the treatment can be planned. Biological peculiarities of various mammary tumours cannot be assessed without grading[5]. This study is aimed at diagnosing the mammary tumours by histopathology and grading them by modified Elston and Ellis method [4].

## 2. Materials and Methods
### 2.1 Samples
Sixteen excisional biopsy samples from dogs having tumour growths, presented at Kerala Veterinary and Animal Sciences University hospitals at Thrissur were collected in 10% neutral buffered formalin. Clinical history including age, sex, breed and size of the tumour was also collected.

### 2.2 Histopathology
The tumour tissues were fixed in 10%neutral buffered formalin for 24 hours. After fixation, the tissues were cut into pieces of 2mm thickness and were washed under running tap water overnight. The tissue samples were dehydrated by passing through ascending grades of isopropyl alcohol, cleared in xylene and embedded in paraffin. Sections of 4-5µ thickness were cut from the blocks and taken on glass slides. The sections were stained with haematoxylin & eosin and observed under the light microscope. Classification of the tumours was done based on the histological characteristics [6].

### 2.3 Grading
The histological malignancy grading (HMG) was done using the modified numeric method of Elston and Ellis for grading human breast cancers, adapted to canine mammary tumors [2].

#### 2.3.1 Tubule formation
Tubule formation in the section was assessed semi quantitatively and a score of one point was given when more than 75% of the area was composed of definite tubules. Two and three points were given respectively when 10-75% and < 10% of the area was covered by tubules.

**2.3.2 Nuclear pleomorphism:** When the nuclei were small with minimum variation in size and had uniform chromatin, a score of one point was given. Nuclei larger in size with moderate anisokaryosis were given 2 points. When nuclei were vesicular and varying considerably in size and shape and bearing prominent nucleoli, 3 points were given.

#### 2.3.3 Mitotic counts
Mitotic activity was assessed at a magnification of 400x(high power field, HPF), which provide a field area of 0.237 sq.mm [10]. A minimum of 10 fields were examined. Upto 9 mitoses per 10 HPF were given 1 point, 10-19 mitotic figures were scored 2 points and 20 or more mitotic figures per 10HPF were given 3 points.

After scoring in each of the above aspects, the scores were added to get a number between 3 and 9. Then the grade was allocated as below:-

HMG I (low) - 3 to 5 points, well differentiated

HMG II (intermediate) - 6 or 7 points, moderately differentiated

HMG III (high) - 8 or 9 points, poorly differentiated

### 3. Results
Histopathological examination of the stained tissue sections revealed that out of the 16 tumour cases, 2(12.5%) were benign and 14(87.5%) were malignant. The mean age of the dogs diagnosed with malignant tumour was 7.86±1.88. Benign tumours were diagnosed as fibroadenoma and the malignant variants included ductal carcinoma (Fig.1), cystic papillary carcinoma, tubulopapillary carcinoma, solid carcinoma (Fig.2), comedocarcinoma (Fig.3) and carcinoma arising in benign mixed tumour (Fig.4). The 14 malignant cases were classified into 3(21.4%) HMG I, 8(57.2%) HMG II and 3(21.4%) HMG III tumours (Table 1).

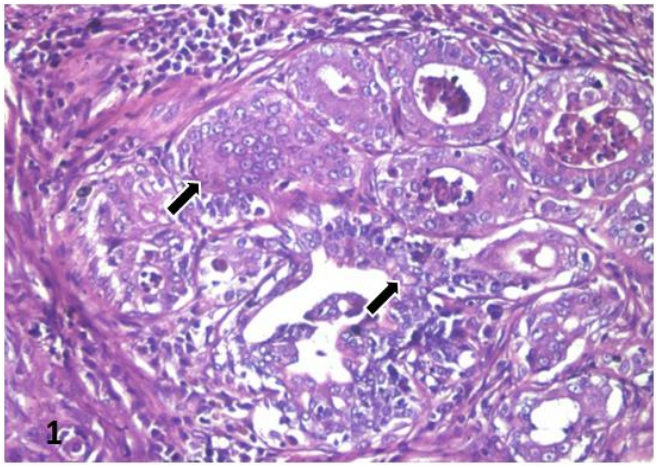


**Fig 1:** Ductal carcinoma. Grade I. Multilayered proliferating neoplastic ductal epithelial cells (arrows). H&E x200;

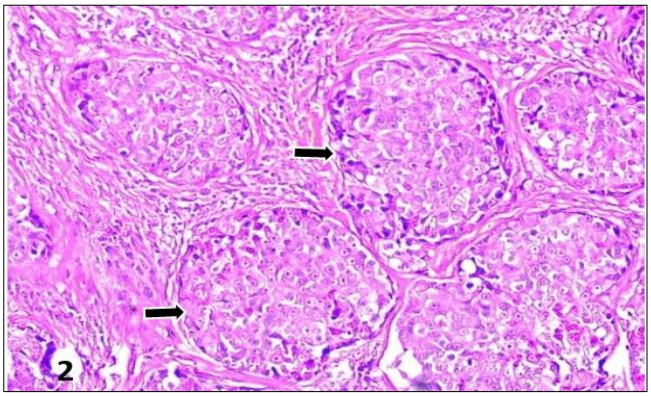


**Fig 2:** Solid carcinoma. Grade III. Closely packed cells form dense irregularly sized lobules without lumina (arrows) supported by fine fibrovascular stroma. H&E x200;

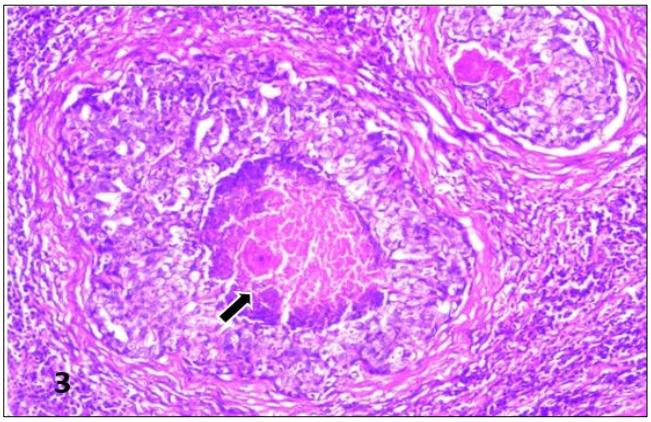


**Fig 3:** Comedocarcinoma. Grade III. Presence of necrotic area (arrow) in the centre of neoplastic cell aggregates. H&E x200;

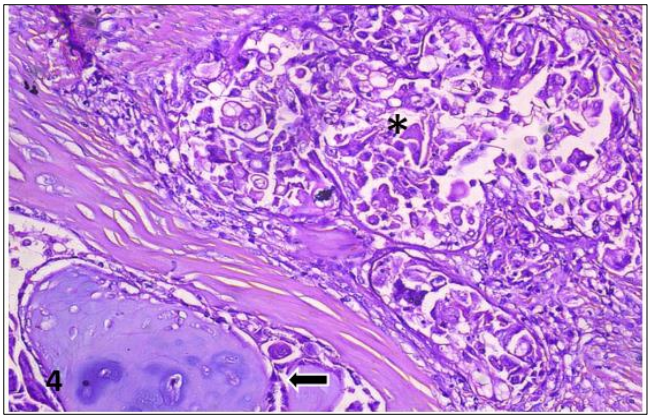


**Fig 4:** Carcinoma arising in benign mixed tumour. Grade I. The chondroid component is benign(arrow), but the neoplastic epithelial cells show moderate pleomorphism(asterisk). H&E x200.

**Table 1:** Grade wise classification of the various subtypes of mammary tumours

| Type | Grade I | Grade II | Grade III | Total |
|---|---|---|---|---|
| Ductal carcinoma | 2 | 3 | 0 | 5 |
| Cystic papillary carcinoma | 0 | 1 | 0 | 1 |
| Tubulopapillary carcinoma | 0 | 1 | 0 | 1 |
| Solid carcinoma | 0 | 0 | 1 | 1 |
| Comedocarcinoma | 0 | 0 | 2 | 2 |
| Carcinoma arising in benign mixed tumour | 1 | 3 | 0 | 4 |
| Total | 3 | 8 | 3 | 14 |

## 4. Discussion

Fibroadenoma consisted of tubules lined by epithelial cells and an abundant stroma of loose connective tissue surrounding the tubules. The tubules are lined by cuboidal or columnar cells with round nuclei. Ductal carcinoma is the tumour that shows ductal differentiation and is the malignant variant of ductal adenoma. The neoplastic epithelial cells showed anisocytosis and anisokaryosis and evaded the basement membrane. Tubulopapillary carcinoma consisted of neoplastic tubules with papillae extending into the tubular lumina. Cystic papillary carcinoma is the type of mammary carcinoma in which the tubular lumina is cystic and dilated with papillae extending into it. In solid carcinoma the cells were arranged in masses without lumina. The closely packed cells formed dense irregularly sized lobules supported by fine fibrovascular stroma. The nuclei were hyperchromatic with a centrally oriented single basophilic nucleolus. Solid carcinomas often metastasize to regional lymph nodes [6]. Comedocarcinoma is a variant of solid carcinoma, which was characterized by the presence of necrotic area in the centre of neoplastic cell aggregates. The necrotic area contained abundant eosinophilic material mixed with cell debris, neutrophils and macrophages. Comedocarcinoma also found to metastasize to regional lymph nodes [6]. In carcinoma arising in benign mixed tumour, the benign part of the tumour was detectable in the tissue whereas the epithelial cells showed features of malignancy.

Identification of prognostic variables and prediction of the biological behavior of the tumours is a major challenge for any veterinary oncologist [11]. A modified version of numeric method of Elston and Ellis is widely adopted for grading of canine mammary tumours. In human medicine, a combination of histological type and grade is used for correct assessment of prognosis of breast cancer. In the present study it was found that majority of the simple carcinomas (most malignant type) were grade III or II. It was in agreement with the previous observations in canines [1] and humans [3]. It was shown in some studies that half (42-55%) of the surgically removed mammary tumors in bitches were malignant [13]. Simeonov and Stoikov (2006) reported that 19% of the canine mammary tumours were benign and 81% were malignant [12]. Goldschmidt (2011) reported that about 20-80% mammary tumors were malignant [9]. In the current study, it was observed that 87.5% (n = 14) of the mammary tumours were malignant. The survivability rate of dogs diagnosed with mammary tumour varies depending on the grade of the tumour [8]. Dogs with undifferentiated carcinomas (grade III) have worse survival rate than dogs with differentiated carcinomas (grade I or II). Simple carcinomas are most dangerous and have a worse prognosis than other carcinomas. Follow up of the cases in the present study has revealed that all the grade III tumours have recurred after an average period of 6 months.

## 5. Conclusion

Grading of the mammary tumours is a practically feasible method for indicating the prognosis of the condition. The grade obtained can be correlated with histopathological classification for assessment of biological aggressiveness and charting out a successful treatment regimen. Present study was successful in identification of the tumour variant and their biological behaviour. Further, the grade of the tumours became the yardstick for adjuvant chemotherapy and rigorous follow up of the cases, especially in high grade tumours.

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