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## Occurrence and pathology of canine mammary neoplasms- A prospective study

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**Abstract**

Prospective studies were carried out from July, 2017 to December, 2017 on 30 clinical cases of canine mammary neoplasms. The median age of occurrence of mammary neoplasm was 9.5 years (range 3-15 years) with highest occurrence in the age group of 9 to < 12 years (56.67%). The median age of occurrence of benign mammary neoplasms was 9 years (4-12 years) and that of malignant mammary neoplasms was 10 years (3-15 years). The occurrence of neoplasms was more in pure breeds (19/30) than in non-descript dogs (10/30). Among the pure breeds, Labradors were most affected, followed by German shepherd, Pomeranian and Spitz breeds. All the cases were recorded only in intact females. Single gland involvement was seen in majority of the cases (25/30, 83.33%) than multiple glandular involvement. The gland on the left side were more affected (22/39, 56.41 %) compared to the right side (17/39, 5.59 %). Inguinal pair was most affected, followed by caudal abdominal and cranial abdominal pairs. Based on histological features, of the 30 cases, 18 (60 %) were of malignant type and 12 (40 %) of benign type. Among the benign neoplasms, benign mixed mammary tumor had the highest occurrence (5/30) followed by fibromyxoma and fibroadenoma (2/30) and solitary cases of complex adenoma, duct papilloma and myoepithelioma. Among the malignant neoplasms, simple carcinomas of various subtypes had the highest occurrence (7/30) followed by carcinoma in mixed tumor (3/30), carcinosarcoma (2/30), comedo carcinoma (2/30), and solitary cases of fibrosarcoma, intraductal papillary carcinoma, complex carcinoma and anaplastic carcinoma.

**Keywords:** canine, mammary neoplasm, prospective study, occurrence, pathology

**Introduction**

In recent years, cancer prevalence has increased among companion animals. This may be due to advances in both human and veterinary medicine that makes pets, like human beings to live longer [1]. Most relevant is the fact that veterinary medical care has made great advances to make canine health care second to that of humans [2]. This trend is one of the suggested theories for the rise in cancer in pets over the last few years [1]. Apart from this, even environmental factors like pollution, radiation, and various life-style associated factors like diet and obesity, also have a major influence on the exponential increase of cancer incidence among pets, as in humans. It is estimated that one out of every four dogs, greater than 2 years of age, dies of cancer with certain popular breeds being over-represented in terms of cancer incidence and mortality [3, 4]. Such an increased incidence of cancers in small animals is motivating further studies in the field of tumor pathology with an aim to increase the survival time and to improve the quality of cancer patients life [5]. In dogs, mammary neoplasms constitute the overall second most frequent neoplasia, surpassed only by skin neoplasms and rank first among bitches especially in sexually intact ones. Based on their histological and biological features, it can be estimated that approximately one third to half of the surgically removed canine mammary neoplasms are malignant [6]. Canine mammary neoplasms, like other neoplasms, are a disease entity with a multi-factorial etiology. The impact of certain endogenous factors of genetical, immunological and hormonal nature is very important in mammary carcinogenesis [6]. Mammary neoplasms may also arise due to several exogenous factors of mechanical, chemical, viral and dietary origin. Apart from these, various other host related factors like breed, age, sex, obesity, intactness and vitamin D status have been associated with the risk of developing mammary neoplasms. The present prospective study reports the occurrence of mammary neoplasms in dogs and their association with age, sex, breed, gland intactness along with the gross and histopathological features.

## Materials and Methods

A total of 31 tissue samples, clinically suspected as canine mammary neoplasms were collected between July 2017 to December 2017 from intact female dogs presented at to the Small Animal Unit- Surgery (SAU-S) of Teaching Veterinary Clinical Complex, RIVER, Puducherry (n=8) and also from Private veterinary practitioners (n=23). The neoplasms were examined for its location, size, shape, color, consistency, gland(s) affected, attachment to the underlying tissues, involvement of regional lymph node and presence or absence of infection. For histopathological study, representative tissue samples from the neoplasm (collected by standard biopsy procedures) were fixed in 10% neutral buffered formalin and processed by routine paraffin embedding techniques. The tissue sections of 4-5  $\mu\text{m}$  thickness were stained with haematoxylin and eosin (H & E) following the procedures [7].

## Results and Discussion

Out of the 31 cases clinically suspected for neoplasm, based on histological features, one case was identified as chronic mastitis and the other 30 cases classified [8] as canine mammary neoplasms, 12/30 (40%) as benign and 18/30 (60%) as malignant neoplasms. The median age of occurrence of canine mammary neoplasms was 9.5 years (range 3-15 years). Highest occurrence (n=17, 56.66%) was recorded in the age group of 9 to 13 years, followed by above 2 to 6 years (n=6, 20%), 6 to 9 years (n=4, 13.33%) and above 13 years (n=3, 10%). The median age of occurrence of benign neoplasms was 9 years (range 4-12 years) and that for malignant was 10 years (range 3-15 years). Age-related occurrence of canine mammary neoplasms observed in the present study is consistent with the report of various earlier studies that the occurrence of mammary neoplasms ranged from 2-16 years with a median age of 10.8 years [9, 10]. The sequential carcinogenic steps that are required for the neoplastic transformation of normal tissues develop over several years and thus malignant cancers are more likely to become manifest in older individuals by a process of natural selection [10]. It has been stated that canine mammary tumors transform over a protracted period of time from benign to malignant, resulting in more number of malignant neoplasms in advanced aged animals [11]. These postulations explain the higher occurrence of malignant mammary neoplasms in advanced aged dogs.

Pure breeds were proportionately more affected (19/30, 63.33%) than mongrels (10/30, 33.33%) and cross bred dogs (1/30, 3.33%). Labrador Retrievers were more affected followed by German Shepherds, Pomeranian and Spitz breeds. Solitary cases were recorded in Weimaraner, Rajapalayam, Pug, Great Dane, Rottweiler, and Golden Retrievers. These observations are in agreement to earlier reports [12, 13] that pure breed dogs were at higher risk of developing mammary tumors than crossbreds and mongrels. Although, the reasons for this natural predisposition of certain breeds are not known, it can be explained to some extent that dogs do inherit abnormal genes (oncogenes) when they are selected for certain genetic traits for desirable morphological features of a particular breed over a period of time [11]. Breed predisposition of mammary neoplasms observed in the present study also varied from the reports of other workers and could be attributed to the fact that different geographical areas have different pattern of breed distribution and their presentation to the hospitals/ clinician.

It is well established that intact dogs are at more risk of

developing mammary neoplasia than spayed bitches [14]. In the present study all the cases were recorded only in intact female dogs. The higher incidence of mammary neoplasm in intact bitches could be attributed to the influence of steroid sex hormones like oestrogen and progesterone, over the mammary tissue during regular oestrous cycles. Both oestrogen and progesterone are mitogenic by their autocrine or paracrine mechanisms. Since steroids regulate the expression of certain cyclins or kinase inhibitors, they may also control cell cycle progression directly [14].

Among the five pairs of mammary glands, neoplasms were recorded from all the glands involving both the sides in different cases. Out of 39 growths from 30 animals, the left side was more involved (22/39, 56.41%) than the right side (17/39, 43.58%). Growths were recorded from a single gland in 25 cases (25/30, 83.33%) and in multiple glands in 5 cases (5/30, 16.67%). The inguinal pair, was most affected (12/39, 30.77%), followed by caudal abdominal (11/39, 28.21%), cranial abdominal (7/39, 17.95%), caudal thoracic (15.38%, 6/39) and cranial thoracic (7.69%, 3/39,) pairs. Overall, the caudal glands (cranial abdominal, caudal abdominal and inguinal) were more affected accounting for 76.93% of the cases. The involvement appeared to progressively increase from the cranial abdominal to caudal abdominal and finally to the inguinal glands. An increasing frequency of occurrence of mammary tumors from cephalad to the most caudal glands has been reported earlier [11, 12, 15]. It has been reported that the posterior pair of mammary glands are more prone to trauma when the animal moves or when it lies down and this may be the reason for more propensity of tumor development in these glands [16]. An increase in tumor occurrence from anterior to posterior mammary gland may be related to the greater growth rate, weight, lobularity, and secretion in the posterior glands compared with the anterior ones [17, 18]. Multiple mammary glands involvement has been reported as a common clinical feature canine mammary tumors [19]. This feature was observed in five cases in the present study. This may be explained by the multi-centric origin of mammary tumors, wherein each tumor will have their own paths of tumor initiation and progression. Although some of them might have similar origin, they present different final picture as they gradually acquire additional genetic changes during tumor progression that results into different morphological features of individual tumors [19].

There exists a high degree of uncertainty regarding histological classification of canine mammary neoplasms, with lot of disagreement among various workers. Although the classification of canine mammary tumors endorsed by the World Health Organisation [8] is widely accepted and followed, owing to difficulty in classifying certain cases recorded in the present study, the 2011 classification system [7] was adopted for the histological classification. The diagnosis of one type or another was often largely dependent on the specific plane of section or the number of sections taken through a particular tumor and type of neoplasm. Out of 30 cases with neoplasms, eighteen samples (60%) were of malignant type and twelve (40%) were of benign type. The 12 benign mammary neoplasms were categorized into different histological types as fibroadenoma (n=2), fibromyxoma (n=2), myoepithelioma (n=1), benign mixed mammary tumor (n=5), duct papilloma (n=1), complex adenoma (n=1) and are shown in Figs. 1-8. Majority of the cases were seen in animals in the age group of > 9-<13 years (n=8) and the rest in >2- <6 years (n=2) and >6- <9 age group (n=2). It has been reported



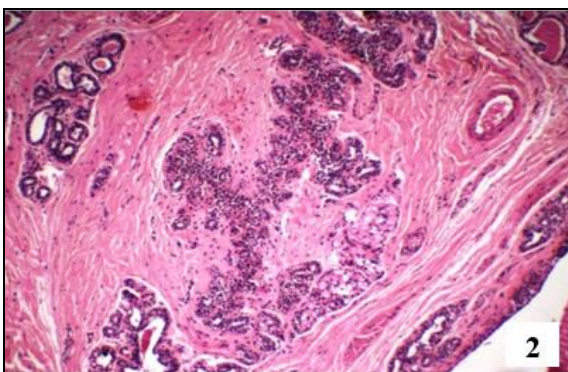
that benign mixed tumors are the most common type of benign mammary tumors in dogs [20]. The 18 malignant mammary neoplasms were categorized as simple carcinomas [Simple adenocarcinoma (n=1), papillary cystadenocarcinoma (n=3), papillary adenocarcinoma (n=1) and tubulo-papillary adenocarcinoma (n=2)], comedocarcinoma (n=2), carcinoma in mixed tumors (n=3), anaplastic carcinoma (n=1), fibrosarcoma (n=1), intra-ductal papillary carcinoma (n=1), carcinosarcoma (n=2), complex carcinoma (n=1) and these are represented in Figs. 9-18. The median age of occurrence of malignant neoplasms was 10 years, majority of the cases were in the age group of > 9-<13 years (n=9) followed by in > 2-<6 years (n=4), >6-<9 years (n=2) and > 13 years age group (n=3). The percentage of malignant neoplasms observed in the present study are in accordance with earlier reports.<sup>12,13</sup> Although the usual incidence of malignant mammary tumors is 50%, there actually exists a wide range based on the population type and size being studied<sup>[14]</sup>.

The malignant mammary neoplasms of epithelial origin (carcinomas) are most common in dogs and their average relative frequency of occurrence among all mammary tumors is 30%<sup>[15]</sup>. The prognosis for the different morphologic forms of carcinoma were significant, with the poorest prognosis (that is, the shortest survival times) being associated with anaplastic carcinomas<sup>[11]</sup>.

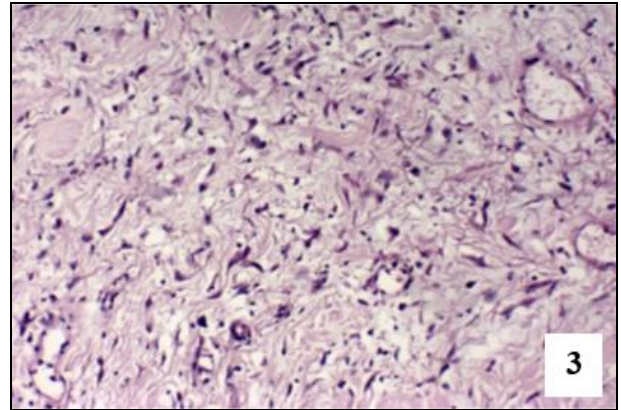
Although, there is considerable advancement in the knowledge on the biology and behavior of canine mammary neoplasms, histological evaluation remains the cornerstone for classifying and grading the neoplasms. Large scale multi-institutional studies on the histopathological classification coupled with molecular subtyping<sup>[21]</sup> along with digital image analysis would provide a better understanding of the microarchitectural details that could be employed as prognostic indicators of canine mammary neoplasms.



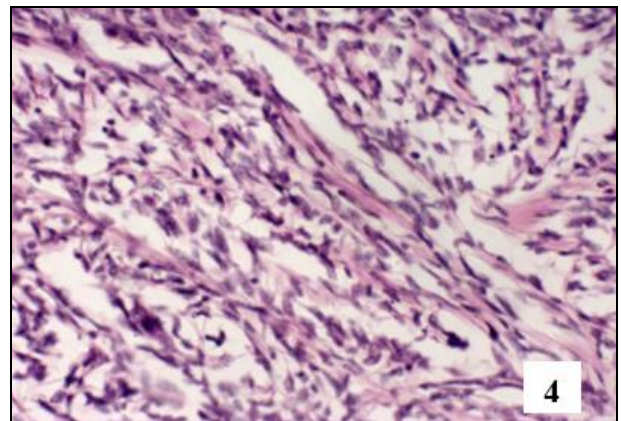
**Fig 1:** Fibroadenoma-Soft growths involving left caudal thoracic and left caudal abdominal glands.



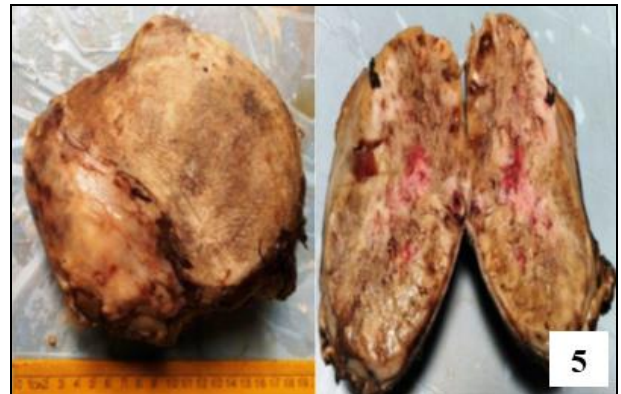
**Fig 2:** Fibroadenoma-Proliferation of collagen rich fibrous tissue and glandular tissue. H&E x100



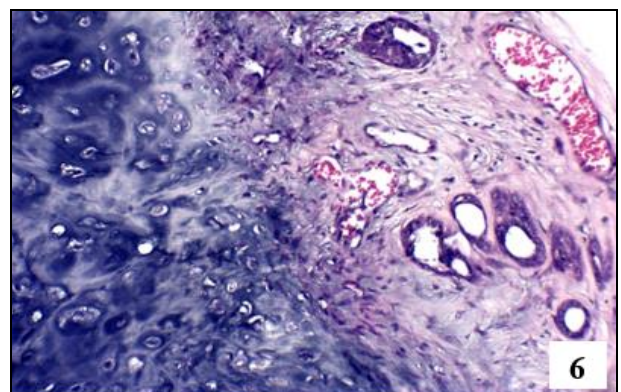
**Fig 3:** Fibromyxoma-Stellate shaped fibroblasts arranged in loose connective tissue matrix. H&E x200



**Fig 4:** Myoepithelioma-Proliferation of spindle shaped myoepithelial cells involving the glandular components. H&E x200

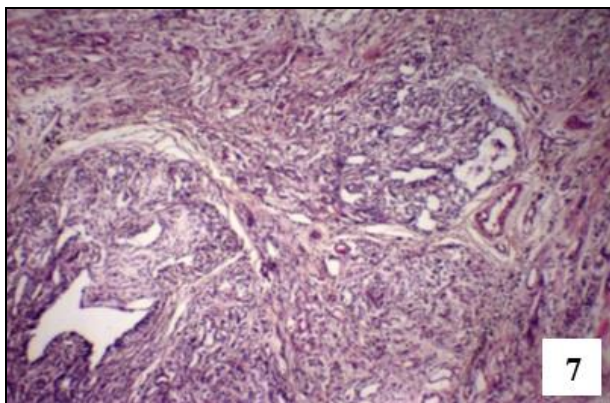


**Fig 5:** Benign mixed tumor- Large, round hard mass that weighed 1.5 kg, tough to cut and grayish white cut surface.

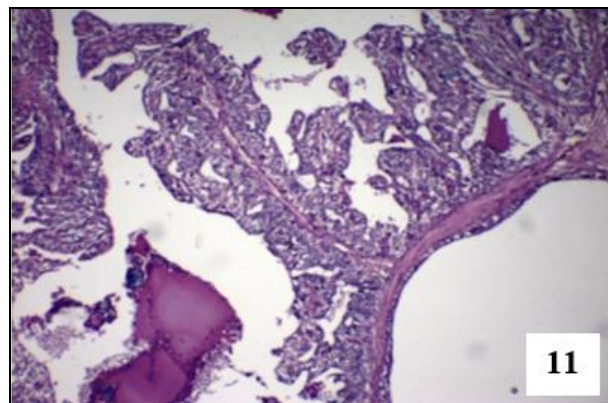


**Fig 6:** Benign mixed tumor-Extensive proliferation of connective tissue. H&E x200

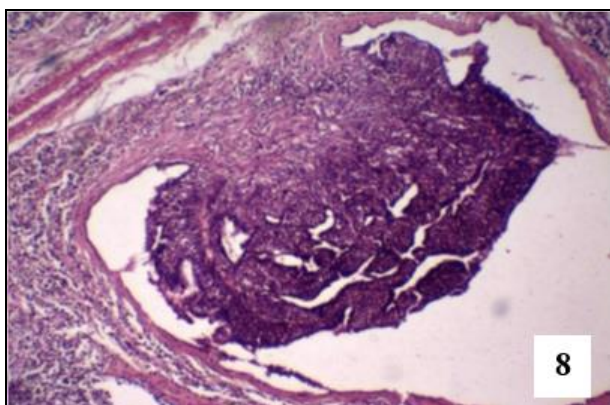




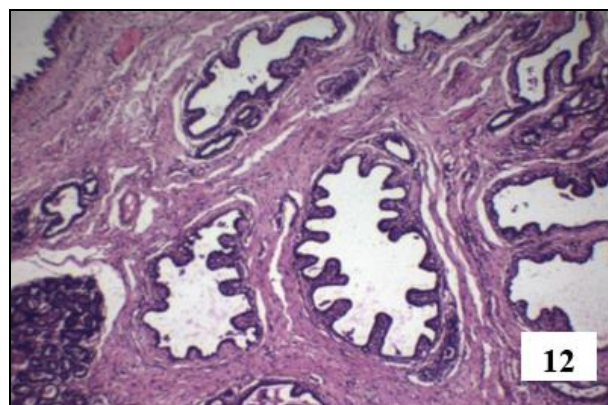
**Fig 7:** Complex adenoma- Proliferation of epithelial cells and myoepithelial cells. H&E x100



**Fig 11:** Papillary adenocarcinoma- Proliferation of glandular epithelial cells forming papillary growths into the lumen. H&E x100



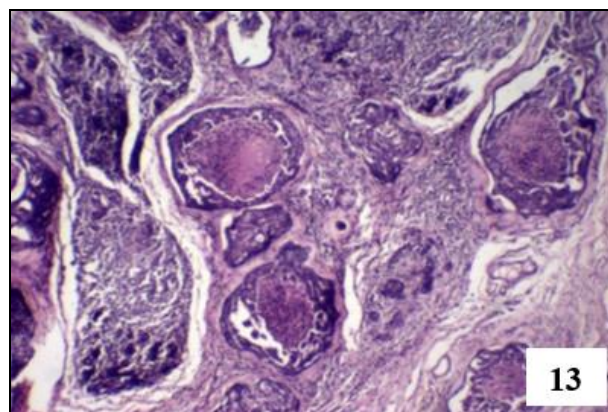
**Fig 8:** Duct papilloma-Proliferation of ductal epithelial cells forming papillary growths into the lumen. H&E x100



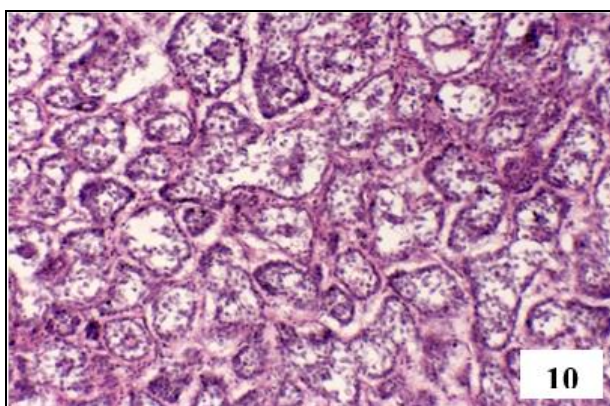
**Fig 12:** Tubulo-papillary adenocarcinoma- Proliferation of glandular epithelial cells forming papillary and tubular patterns. H&E x 100



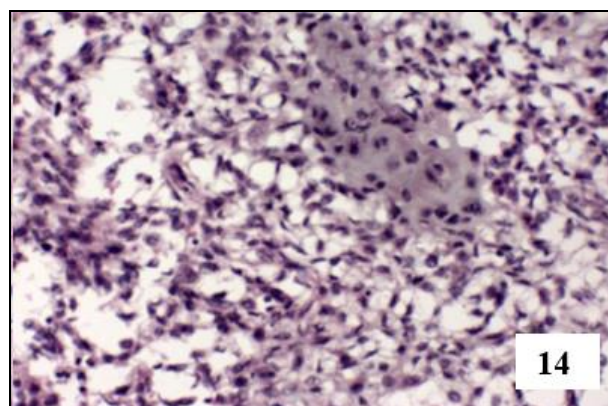
**Fig 9:** Simple adenocarcinoma- Round, large growth with creamy white surface, weighed 300 grams.



**Fig 13:** Comedocarcinoma- Proliferation of lining glandular epithelial cells with central area of necrosis. H&E x400.

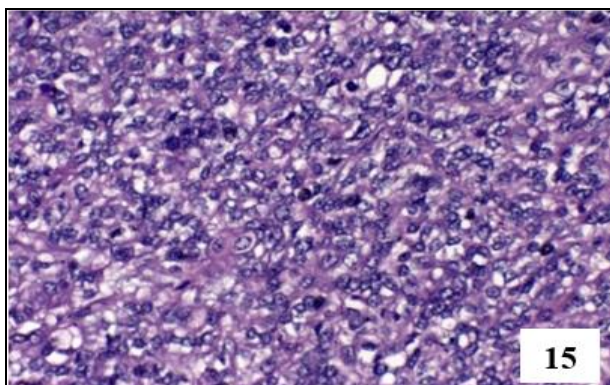


**Fig 10:** Simple adenocarcinoma- Extensive proliferation of well differentiated glandular epithelium H&E x200

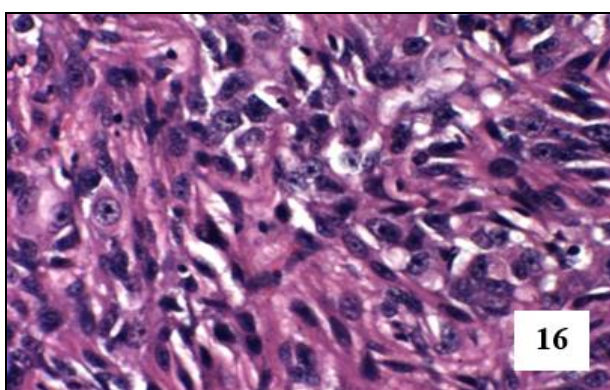


**Fig 14:** Carcinoma in mixed tumor-Myxomatous and chondroid differentiation of connective tissue component. H&E x400

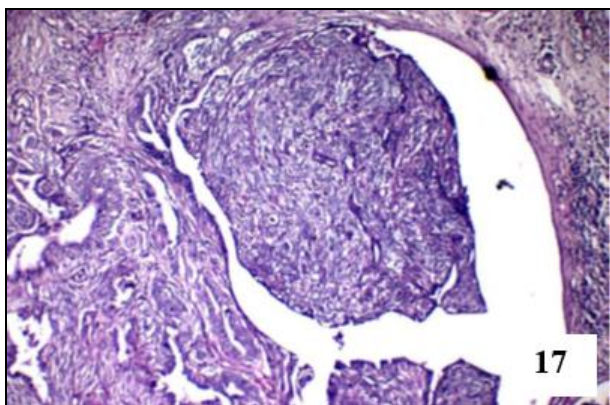




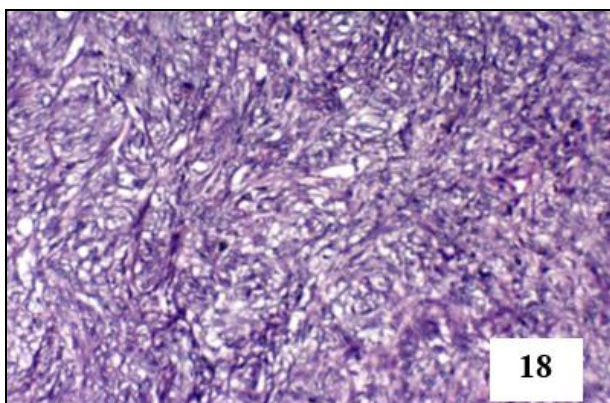
**Fig 15:** Anaplastic carcinoma-Extensive proliferation of undifferentiated epithelial cells in a thin connective tissue support, moderate number of mitotic figures. H&E x 400



**Fig 16:** Fibrosarcoma-Proliferation of spindle shaped immature fibroblasts. H&E x400



**Fig 17:** Intraductal papillary carcinoma- Papillary pattern formed by proliferating epithelial cells into the lumen of the duct. H&E x100



**Fig 18:** Carcinosarcoma- Concomitant proliferation of both epithelial cells and connective tissue components. H&E x200

## Conclusion

The prospective study highlighted the occurrence of canine mammary neoplasm in female dogs with respect to the age, breed and glandular involvement. The gross and histopathological features of benign and malignant mammary neoplasms were described. The findings can be utilized by clinicians for clinical and therapeutic decision making as well as for large scale epidemiological studies.

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