

## Mammary gland tumours in male dogs: a hormonal and tumour marker study

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### ABSTRACT

Seven male dogs with clinically and histologically confirmed mammary gland tumours were included in this study. All dogs were sexually intact. Median age at diagnosis was 9.4 yrs. Five were purebred and the rest were mongrels. Six dogs had a solitary growth whereas in one animal multiple growths were seen. All tumours were histologically benign. Simple adenomas with mixed acinar and papillary pattern were observed. All tumours were removed surgically. Healing was perfect in all cases without any postoperative complications. No recurrence was recorded up to six months post-surgery. The expression of sex hormones and p53, cox-2 and MMP-7 tumour marker genes was strong in the majority of cases. Although uncommon, mammary tumours do occur in male dogs.

**Key words:** dog, male, mammary tumour, surgery, tumour markers

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### Introduction

Cancer has gained considerable relevance in animals recently owing to the increased awareness among people of animal suffering and pain. The diagnosis and management of neoplasms, therefore, represents a major challenge faced by veterinary oncologists. Mammary gland tumours are among the most common canine neoplasms, but the vast majority of these tumours occur in intact female dogs (BRODEY et al., 1983; KHIMTA et al., 2010). In canines, mammary gland tumours that occur in males range from 0-2.7% (average <1%) (MOULTON et al., 1970). Sex hormones play a vital role in the occurrence of mammary gland tumours. The p53 gene over expression is an independent factor

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indicating worse prognosis in canine mammary gland tumours (LEE et al., 2004). The p53 may be a useful prognostic marker for evaluating malignancy in canine mammary gland tumours (ILHAN et al., 2008). There is a strong positive correlation between expression of cyclooxygenase-2 (cox-2) and the grade of malignancy in the tumour. Increased cox-2 expression is linearly related to worse prognosis and shorter overall survival of the canine mammary gland tumour patients. Canine mammary gland malignant tumours had the highest values of cox-2 expression (QUEIROGA et al., 2007). Matrix metalloproteinase (MMPs) is a family of zinc and calcium-dependent proteolytic enzymes that degrade macromolecules of the extracellular matrix. Members of this family, such as MMP-2, -9 and -7, have been shown to be associated with tumour progression and invasion in human cancer tissues. Matrilysin (MMP-7) influences the early stage of tumourigenesis (NELSON et al., 2000).

Reports of mammary gland tumours in male dogs are lacking. In this study, seven mammary gland tumours in male dogs are presented.

#### Materials and methods

The study was carried out on seven male dogs of different breeds and ages, with variable sizes of spontaneous mammary gland tumours, which presented at the Institute's Referral Veterinary Polyclinic. Details of these cases are given in Table 1.

Table 1. Animal case history

Sl No	Animal	Breed	Age (yr)	Sex	Tumour location (tumour size)	Histology(predominant pattern)
1	Dog	German shepherd	10	Intact male	Tumour at level of prepuce (9 cm in diameter)	Simple adenoma (papillary)
2	Dog	Spitz	8	-do-	Tumour at right of prepuce (5 cm in diameter)	Simple adenoma (acinar)
3	Dog	German shepherd	11	-do-	Tumour at right of prepuce (7 cm in diameter)	Simple adenoma (acinar)
4	Dog	Mongrel	9	-do-	Tumour at left abdominal (9 cm in diameter)	Complex adenoma (acinar)
5	Dog	Doberman	10	-do-	Tumour at level of prepuce (8 cm in diameter)	Simple adenoma (acinar)
6	Dog	Cocker Spaniel	7	-do-	Tumour at left of prepuce (7.5 cm in diameter)	Papillary fibroadenoma
7	Dog	Mongrel	11	-do-	Tumour at left caudal (6 cm in diameter)	Simple adenoma (papillary)

Thoracic radiographs were taken in all these patients to detect the possible presence of lung metastasis. Tumour biopsy samples were collected before any therapy, fixed immediately in 10% neutral buffered formalin and processed routinely by paraffin embedding technique. Sections of 4-5 microns thickness were cut and stained by haematoxylin and eosin (H&E) for histopathological examination.

The levels of oestrogen and progesterone were estimated in serum samples with radio-immune assay (RIA) kit (Immunotech SAS-130 France). Samples and calibrators were incubated for 3 hours with  $^{125}$ I-labelled estradiol, as tracer, in antibody coated tubes. After incubation, the content of the tubes was aspirated, and bound radioactivity was measured. A calibration curve was established and unknown values were determined by interpolation from the curve.

The expression of enzyme matrilysin/MMP-7 (matrix metalloproteinase) genes was assessed after collecting the tumour tissues from the affected male animal, as well as from five adult non-descript breeds of normal (CMT unaffected) male dogs by gelatine zymography and RT-PCR. The necessary permission was obtained from the animal's owner, as well as from the Institute's Animal Ethics Committee for collection of normal mammary tissue from the same location of the mammary glands in male animals. For gelatine zymography, homogenized tumour tissue was prepared using a REMI homogenizer, and the crude extract was mixed with 5X sample/gel loading buffer in a 5:1 ratio, and loaded into the wells of gel casting, fixed into vertical slab, gel electrophoresis apparatus. Electrophoresis was carried out at room temperature with constant voltage mode at 100 V. This was followed by incubation of the gel in 2.5% Triton X - 100 solutions at room temperature for 3 hours, and later in developing buffer at 37 °C for 18 hours. Following this the gel was stained with 0.25% coomassie blue for 2 hours and destained in deionized water. RT-PCR for MMP-7 gene expression was carried out with the gene specific primer namely F: 5'- GATGTGGTGTGCCTGATGTC-3' and R: 5'-CTCCTCTTGCAAAGCCAATC-3' with a primer concentration of 20 picomols, as per the method described by SAMBROOK and RUSSELL (2001). The expression profiling of p53 and cox-2 genes in mammary tumour affected male dogs was determined using Reverse Transcriptase PCR with gene specific primers for p53, namely: F: 5'-GCGGCCCATCCTCACTATC-3' and R: 5'-CACAAACGCGTACCTCAAAGC-3' and with gene specific primer for cox-2 gene namely: F: 5'- ATGGGTGTGAAAGGCAAGAAA-3' and R: 5'-GGTAAAGTGCTGGGCAAAGAAT-3' with a primer concentration of 5 picomols for each gene. RPL was used as a house keeping gene (endogenous control) for the analysis of data. The total RNA was isolated from mammary tumours using Tri-reagent (Sigma, USA) as per the manufacturer's instructions. Each DNase treated total RNA sample (1 µg) was reverse transcribed with a suitable negative and positive control, using the IScript DNA synthesis kit (BIORAD) according to the manufacturer's instructions.

Surgical therapy was performed in all animals after confirming the histological nature (benign) of the tumorous growth. The owner's consent was also taken into consideration before surgical therapy. All the cases were under surveillance for six months post-surgery for any recurrence, if any, by regular telephone conversations with the pet owners.

The data pertaining to various parameters studied in canine cancer patients were analysed using the 'paired-t' test and analysis of variance (ANOVA) as per standard statistical methods.

Necessary permission was obtained from the Institute's Animal Ethics Committee (IAEC) to conduct this research on clinical cases.

### Results

History revealed that these tumours developed vigorously within a very short period of time. Out of 7 animals, solitary tumours were seen in six animals (Fig. 1, 2), whereas multiple small tumours developed in one animal. The majority of tumours were well circumscribed and pedunculated except two, where ulcerated lesions were observed. Grossly, the mammary gland tumours were soft to firm in consistency, tan to off-white in colour, pedunculated, sessile or subcutaneous masses that ranged from 6-9 cm at their largest dimension. Most of the mammary gland tumours were observed in the 4<sup>th</sup> (caudal abdominal) and 5<sup>th</sup> (inguinal) mammary glands.



Fig. 1. Mammary tumour in a male dog



Fig. 2. Mammary tumour in another male dog

Lateral radiography of the thorax of the male dogs affected by mammary gland tumours revealed no radio-opaque, soft tissue scattered lesions in the lungs.

All the cases that underwent surgery had an uneventful recovery. The animals appeared quite alert and responsive throughout the postoperative period. Postoperative complications, such as herniation, stitch abscess, peritonitis etc. were not observed in any case. Complete wound healing was observed on the 12-15<sup>th</sup> day post-surgery. No sign of any recurrence was observed up to six months post-surgery.

Histologically, all but one tumour were diagnosed as simple adenoma. A simple adenoma is characterized by single or multiple well circumscribed nodules, composed of numerous acinar structures and papillary projections, lined by a single or multiple layers of cuboidal to columnar epithelium. The neoplastic cells were supported by a moderately thick fibro-vascular stroma. The majority of simple adenomas were arranged predominantly in an acinar pattern, with large areas of papillary growth. All mammary gland tumours have a continuous layer of spindle-shaped myoepithelial cells immediately subjacent to the epithelial layer lining acini and papillary projections (Fig. 3, 4). The single case of complex adenoma was characterized by acinar adenomatous growth, punctuated by several small islands of spindled myoepithelial cells, in a myxomatous matrix (Fig. 5).

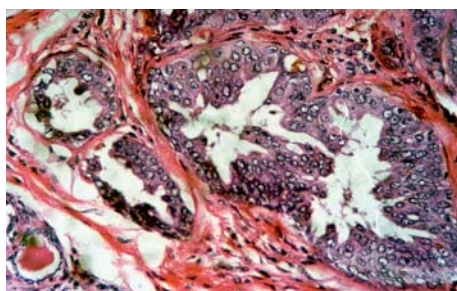


Fig. 3. Papillary adenoma

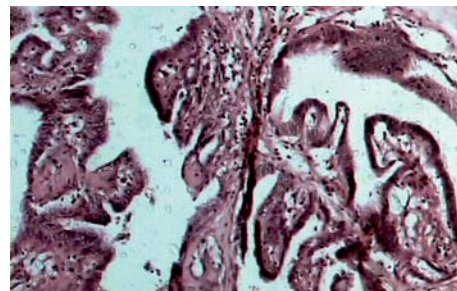


Fig. 4. Papillary acinar adenoma

The serum oestrogen value analysed in these male animals with mammary gland tumour was found very high. The level of estradiol was found to be  $978 \pm 26$  pg/mL (mean  $\pm$  SE) in dogs with mammary gland tumours. Similarly, serum progesterone value in male dogs with mammary gland tumours was also found high. The mean  $\pm$  SE value of progesterone was found to be  $2.16 \pm 0.58$  ng/mL versus the basal value of  $<1$  ng/mL.

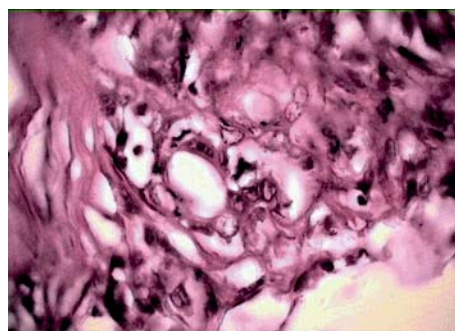


Fig. 5. Complex adenoma

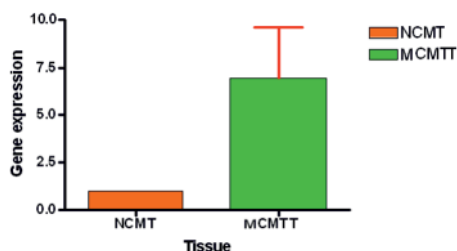


Fig. 6. Relative gene expression of p53 gene. NCMT-normal canine mammary tissue; MCMTT-male canine mammary tumour tissue.

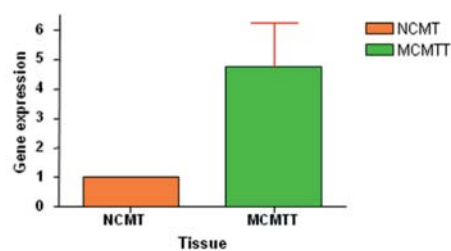


Fig. 7. Relative gene expression of Cox-2 gene

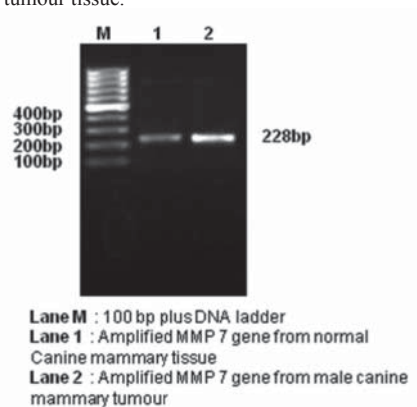


Fig. 8. PCR amplification of MMP7 gene

Higher levels of p53 gene expressions were detected in 4 out of 7 (57.14%) animals when compared with normal mammary tissues. Mean p53 expression levels of mammary gland tumour and normal mammary tissue were  $4.57 \pm 1.44$  and  $1.00 \pm 00$ , respectively. Higher levels of cox-2 gene expressions were also detected in 5 out of 7 (71.42%) cases, when compared with normal mammary tissues. Mean cox-2 expression levels of mammary gland tumour and normal mammary tissue were  $6.25 \pm 1.28$  and  $1.00 \pm 00$ , respectively. Comparing the levels of expression of p53 and cox-2 gene in the male canine mammary gland tumours and the normal mammary tissue, there was a significant increase in the expression of p53 and cox-2 genes in tumour tissue ( $P < 0.05$ ). A relative gene expression level of p53 and cox-2 genes was recorded (Fig. 6, 7). For RT-PCR analysis of MMP-7 in male canine mammary tumour tissue, the total RNA from male canine mammary tumour

tissue was isolated. The ratio of A260/A280 was 1.9, indicating that the isolated RNA was reasonably free of contamination. The RT-PCR products were subjected to 1% agarose gel electrophoresis and the results are shown in Fig. 8. The concentration of amplicon appeared to be high in the tumour samples when compared with that of normal male dog samples. The male canine mammary gland tumour tissues also showed higher levels of expressions of MMP- 7 enzymes in comparison to normal male mammary tissue.

### Discussion

Mammary gland tumours are common in female dogs, accounting for up to 42% of all tumours in the bitch (DORN et al., 1968). Mammary gland tumours in male dogs are far less common, accounting for between 0 and 2.7% of all mammary gland tumours in dogs (MOULTON et al., 1970). The prevalence of mammary gland tumours in female dogs has been associated with age and breed (KHIMTA et al., 2010). The average age of onset for the tumours in male dogs in this study was 9.4 yrs. BEARSS et al. (2012) also reported that the average age of mammary gland tumours in male dog was 9.2 yrs. Like mammary gland tumours in female dogs, most of the mammary gland tumours in male dogs were observed in the 4<sup>th</sup> (caudal abdominal) and 5<sup>th</sup> (inguinal) mammary glands. The reason for this might be that the posterior glands have a greater volume of glandular tissue to react to any carcinogenic stimulus. The higher prevalence of mammary gland tumours in the caudal glands in male dogs is also attributed to the increased mass of mammary tissue in which a tumour might arise, although male mammary tissue is composed of only ductal elements and is devoid of fully developed terminal duct lobular units (BEARSS et al., 2012).

Radiography of the thorax provided information pertaining to the extent of organ involvement and the presence of metastasis in the lungs. Lateral radiography of the thorax in dogs affected by mammary gland tumours revealed no radio-opaque, soft tissue scattered lesions in the lungs, and thereby the involvement of pulmonary metastasis was ruled out in all cases subject to surgical treatment.

In this study, all tumours were removed by surgical excision. Surgery is the first choice for treatment of canine mammary gland tumours, in the absence of metastatic disease and inflammatory carcinoma (CASSALI et al., 2011; MAITI et al., 2011). The complete surgical removal of localized tumours without metastatic involvement is the therapeutic procedure with the highest probability of cure. Surgical excision of mammary gland tumours also allows histological examination, increases survival time, improves the patient's quality of life, modifies disease progression and can be curative (CASSALI et al., 2011).

Histologically, all but one tumour were diagnosed as simple adenomas. BEARSS et al. (2012) reported 27 mammary gland tumours in 18 male dogs and all tumours were histologically diagnosed as benign simple adenomas with mixed acinar and papillary pattern. SABA et al. (2007) also reported all benign mammary gland tumours in 8 male

dogs. This is in contrast to previous reports on mammary gland tumours in male dogs, in which 28 of 51 were classified as malignant (JABARA, 1969; MITCHELL et al., 1974).

All male dogs affected by mammary gland tumours showed a higher expression of oestrogen and progesterone concentrations. These findings correlated with the etiological factor in the occurrence of spontaneous canine mammary tumours in male dogs, which appears to be sex hormone dependent. Canine and human mammary gland tumours are hormone dependent, and both benign/malignant canine mammary gland tumours express the oestrogen receptor (ER) (SORENMO, 2003). Though ER as well as PR (the progesterone receptor) is present in almost all histologically normal canine mammary tissues, ER expression remains high in benign tumours (RUTTEMAN et al., 1988) and it is significantly reduced in carcinomas in female dogs. PR expression also showed a progressive decrease from benign to malignant canine mammary lesions (MILLANTA et al., 2005). In this study, all the mammary tumours were benign and hence in agreement with these findings. It could be concluded that it is the presence of these female sex hormones, namely oestrogen and progesterone, that is promoting the growth of these tumours in male animals.

In this study, higher levels of p53, cox-2 and MMP-7 gene expressions were detected in the majority of cases. The presence of a p53 mutation is significantly associated with larger tumour diameter (FAILLE et al., 1994) and p53 mutation is used as a risk factor for increased risk of recurrence and death from breast cancer, independent of tumour size and hormone receptor levels (IACOPETTA et al., 1998). Over expression of the p53 gene in canine mammary gland tumours, in comparison to corresponding normal mammary gland tissue, was also reported by other authors (RUNGSIPIPAT et al., 1999; KUMARAGURUPURAM et al., 2005). The inactivation of the p53 gene, as a result of mutation, is a key step in neoplastic transformation and progression (VELDHOEN et al., 1999). p53 gene protein over expression was found to be a useful predictor of increased malignant potential and poor prognosis in canine mammary gland tumours (LEE et al., 2004). High expression of the cox-2 gene was detected in male mammary gland tumours, in comparison to normal mammary gland tissue. Over expression of cox-2 in human and canine mammary gland tumours was also reported by PRESCOTT and FITZPATRICK (2002). Cyclooxygenase-2 is a potential marker for mammary cancer in woman and dogs, as its expression is higher in tumours with poor prognosis. It inversely correlates with the overall survival rate, which changes the prognosis (LAVALLE et al., 2009). Enhanced cox-2 expression is sufficient to induce mammary gland tumour genesis. Cox-2 over expression in canine mammary gland tumours was associated with a high tumour histological grade, greater tumour metastatic and recurrence rates, and shortened survival time (DORE et al., 2003).

In this study, a high expression of the MMP-7 (matrilysin) gene was detected in male mammary gland tumours, in comparison to normal mammary gland tissue. The



smallest member of the MMP family is MMP-7 (matrilysin), which is mainly expressed by epithelial cells. Matrilysin is one of the matrix metalloproteinase that has a critical role in tumour invasion, and it is often expressed in cancers (ADACHI et al., 1999). Like other MMPs, matrilysin can promote cancer invasion by proteolytic cleavage of the ECM substrates. Matrilysin activates other MMPs, such as proMMP-2 and proMMP-9, to facilitate tumour invasion. Matrilysin influences the early stage of tumour genesis (NELSON et al., 2000).

The exact cause of mammary cancer in male dogs is still obscure. However, some previous reports of mammary neoplasia in male dogs implicated hormonal abnormalities, particularly in association with testicular neoplasm, as the cause of the tumours (JABARA, 1969; RAFLO and DIAMOND, 1980). None of the dog in this study had testicular neoplasia or other testicular abnormalities. Some other risk factors for mammary tumours in males are undescended testis, orchietomy, testicular injury or inflammation, hormonal therapy, high blood cholesterol, rapid weight gain, obesity and diabetes (THOMAS et al., 1992). However, in this study, there was no history of obesity, diabetes or sex hormone therapy in any affected animal.

In summary, mammary neoplasia in male dogs is rare. In this study, middle-aged, intact male dogs of pure as well as mixed breed were affected. Almost all tumours were simple adenomas and histologically benign, without any evidence of recurrence or metastasis. Various tumour marker genes, which include p53, cox-2 and MMP-7, showed higher expressions as compared to normal male dogs. Expression of sex hormones in these male dogs was significantly higher. All tumours were excised surgically and healed uneventfully. However, a larger number of cases is required to study conclusively the possible role of hormones and the correlation between castration and the incidence of male mammary gland tumours.

#### **Declaration of conflicting interests**

The authors declared that they had no conflicts of interests with respect to their authorship or the publication of this article.

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**SAŽETAK**

U istraživanje je bilo uključeno sedam pasa s potvrđenim tumorima mliječne žlijezde, koji nikada nisu opasivali kuje. Njihova prosječna dob kod postavljanja dijagnoze iznosila je 9,4 godina. Pet ih je bilo čistokrvnih, a dva mješanca. U šest je pasa bio ustanovljen solitarni, a u jednoga multipli rast. Svi su histološki bili dobroćudni. Ustanovljeni su adenomi s miješanim acinarnim i papilarnim oblikom. Svi su bili kirurški uklonjeni. Ozdravljenje je bilo potpuno bez ikakvih postoperativnih komplikacija. Tumori se nisu povratno javili šest mjeseci nakon operacije. U većini slučajeva bila je izražena aktivnost šest hormona i tumorskih biljega p53, cox-2 i MMP-7. Iako rijetko, tumori mliječne žlijezde javljaju se i u pasa.

**Ključne riječi:** pas, mužjak, tumor mliječne žlijezde, kirurgija, tumorski biljezi

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