

## Mammary Gland Tumors in Male Dogs

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**Background:** Reports of mammary-gland tumors in male dogs are lacking.

**Objective:** To describe the clinical characteristics of mammary-gland tumors in male dogs.

**Animals:** Eight male dogs diagnosed with mammary-gland tumors.

**Methods:** Retrospective study. Medical databases from 3 institutions were searched. Medical records were abstracted, and owners and referring veterinarians contacted for follow-up information. Tissues were reviewed for histologic type, and immunohistochemical staining for estrogen and progesterone receptors (ER, PR) was performed.

**Results:** Eight dogs with histologically confirmed mammary-gland tumors were included in this retrospective study. Median age at diagnosis was 11.5 years. Four dogs were sexually intact; 4 were neutered. All were purebred. Mammary-gland tumors were incidental findings in 7 of 8 dogs. All dogs were treated with only surgical excision. All but 1 dog had benign epithelial tumors. The dog with the malignant tumor was the only dog to develop possible local recurrence but de novo tumor development cannot be excluded. No dog had evidence of metastatic disease at diagnosis. Based on institutional population data, it was determined that female dogs are 62 times more likely to develop mammary-gland tumors than male dogs ( $P < .001$ ). Estrogen-receptor expression was strong in the majority of tumors; progesterone-receptor expression, although present in all tumors, was less intense.

**Conclusions/Clinical Importance:** This study suggests that mammary-gland tumors in male dogs are rare, usually benign, and surgery alone can provide long-term control in most dogs.

**Key words:** Estrogen receptor; Mammary adenoma; Mammary carcinoma; Progesterone receptor.

Mammary-gland tumors are among the most commonly diagnosed neoplasms in female dogs, but this tumor type is seemingly rare in male dogs.<sup>1</sup> The majority of mammary-gland tumors in female dogs are of epithelial origin, and approximately 50% are malignant.<sup>2,3</sup> Early spaying of female dogs drastically reduces the risk of mammary-gland tumor development, suggesting that sex hormone milieu is an important risk factor.<sup>4</sup> Additionally, several important prognostic factors such as tumor size,<sup>5–7</sup> histologic grade,<sup>2</sup> histologic subtype,<sup>2,5,8</sup> and evidence of metastasis at diagnosis<sup>5–7</sup> have been identified for mammary tumors in female dogs. Approximately 50–77% of epithelial mammary-gland tumors express estrogen receptors (ER), and receptor expression appears to correlate with degree of histologic differentiation. ER positive (ER+) tumors are typically well-differentiated and carry a better prognosis.<sup>9–12</sup>

Breast cancer is rare in men, accounting for less than 1% of all diagnosed malignancies.<sup>13</sup> It typically occurs in older men.<sup>14</sup> Possible risk factors for this disease include increasing age, testicular injury, obesity, gynecomastia,

Klinefelter's syndrome, and a family history of breast cancer.<sup>13,15,16</sup> The majority of these tumors are malignant, and approximately 65–80% are ER+.<sup>17,18</sup> Some studies have indicated that the prognosis for breast cancer in men is worse than that for women;<sup>14,17</sup> however, other studies have found little difference in prognosis between the sexes.<sup>19,20</sup>

Because of the paucity of reported cases of mammary-gland tumors in male dogs, the purpose of this retrospective study was to characterize the biologic behavior and clinical characteristics of these tumors in male dogs.

### Materials and Methods

#### Clinical Data Accrual

Medical databases from Louisiana State University, Texas A&M University, and the University of Wisconsin-Madison Veterinary Medical Teaching Hospitals were searched for male dogs diagnosed with primary mammary-gland tumors from 1994 to 2004. Dogs with complete medical records for abstracting archived paraffin-embedded tumor tissue for histologic review and a histopathologic diagnosis of mammary-gland tumor were included in this retrospective study. Case information was obtained from medical records and from phone calls to owners and referring veterinarians. Data collected included age at diagnosis, breed, neuter status, date of diagnosis, presenting complaint(s), number of mammary-gland tumors, tumor location, tumor size, type of clinical staging tests performed and results of those tests, type of surgery performed (lumpectomy, mastectomy, regional mastectomy, or chain mastectomy), type of adjuvant therapy, histopathologic diagnosis, time to local recurrence, time to metastasis, survival time, and cause of death.

#### Pathology

A single pathologist (SJM) reviewed biopsy samples from all 8 dogs to confirm the diagnosis of primary mammary-gland tumor, determine surgical margins, degree of malignancy, and subtype. These cases were submitted as unstained slides for ER and progesterone receptor (PR) immunohistochemical staining at the University of Tennessee College of Veterinary Medicine (UTCVM)

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**Table 1.** Characteristics of mammary tumors in male dogs.

Histologic Diagnosis	Tumor Size	ER	PR
Complex adenoma	1.5 cm	100%	60%
Simple adenoma	1 cm	60%	50%
Papillary cystadenoma, SCC, mammary lobular hyperplasia	2 cm	85%	50%
Benign mixed mammary tumor	0.8 cm	40%	5%
Complex adenoma	3 cm	60%	50%
Complex adenoma	1 cm	60%	40%
Complex adenoma	1 cm	30%	5%
Benign mixed mammary tumor	2.5 cm	75%	40%

ER, estrogen receptor; PR, progesterone receptor.

immunohistochemistry laboratory. IHC protocols for ER and PR staining were similar to those previously reported.<sup>9,21</sup> Briefly, all slides were deparaffinized and rehydrated through alcohols to water. Antigen retrieval was performed for 20 minutes at 95°C in a pH 6.0 citrate buffer.<sup>a</sup> All slides were soaked in tris-buffered saline (pH 7.6) for 5 minutes before being loaded into the computer-controlled automated stainer.<sup>b</sup> A 3% hydrogen peroxide block was applied for 5 minutes, and this was followed by a 5-minute nonserum protein block.<sup>c</sup> The monoclonal anti-ER antibody,<sup>d</sup> at a 1:20 dilution, was applied and incubated for 30 minutes. Similarly, the monoclonal anti-PR antibody,<sup>e</sup> at a 1:200 dilution, was applied and incubated for 30 minutes. A horseradish peroxidase-labeled polymer system<sup>f</sup> was applied to all slides, which were then incubated for 30 minutes. Slides were then rinsed in tris-buffered saline, and 3,3'-diaminobenzidine chromogen<sup>g</sup> was applied for 10 minutes. After rinsing, all slides were counterstained with hematoxylin,<sup>h</sup> dehydrated, and coverslipped. Appropriate positive control tissue included normal canine mammary gland. Negative control slides included mammary tissue and a representative mammary neoplasm and each processed without primary antibody and with substitution of Universal Negative Control+ rabbit serum.<sup>i</sup> The ER and PR expression was quantified subjectively by determining approximate percentages of neoplastic cells that expressed the receptors at 20× power. Percentages were based on the numbers of positive cells in each field, and roughly 750 neoplastic cells were present per 20× field. In larger tumor sections several fields were counted to better determine percentages of positively staining cells. Each case was compared to the positive control to determine intensity of stain expression. Tissues determined to be strongly positive revealed nuclear expression at or higher than the level detected in the control tissues, whereas weakly positive tissues revealed nuclear expression slightly below that seen in the control tissues, but still clearly recognizable.

### Statistical Analysis

The median time to local recurrence and median survival time were calculated using Kaplan-Meier analysis. Dogs were censored from analysis for the following reasons: (1) loss to follow-up; (2) death before relapse. Statistical calculations were performed using a commercial statistical software package (Prism v4.0b).<sup>j</sup> Annual incidence rates of mammary-gland tumors in female dogs and male dogs were calculated based on number of dogs seen at the University of Wisconsin (UW) and Texas A&M University (TAMU). This information was not available from Louisiana State University. The relative risk of developing mammary-gland tumors in female versus male dogs, as well as relative risk in intact males versus neutered males, was calculated using two-sided analysis with Fisher's exact test.

### Results

Eight male dogs diagnosed with primary mammary-gland tumors were identified. All dogs were purebred. There were 3 Cocker Spaniels, 2 Labrador Retrievers, and 1 each of Basset Hound, English Bulldog, and Rottweiler. The median age of the dogs was 11.5 years (7–13 years). Four dogs were neutered, and 4 were intact at the time of mammary-gland tumor diagnosis.

Mammary masses were incidental findings in 7 dogs (88%); the remaining dog was examined because of the mammary mass. Tumors were located in the caudal glands in 4 dogs, in the cranial glands in 2 dogs, and in the 3rd gland in 1 dog. Histologically, 7 (88%) were benign tumors, including 4 complex adenomas, 2 benign mixed mammary tumors, and 1 simple adenoma (Table 1). One dog had a malignant tumor that was papillary cystadenoma with transformation to squamous cell carcinoma and peripheral mammary lobular hyperplasia.

All dogs were treated with surgical excision alone. Surgeries performed included lumpectomy (7) and regional mastectomy (1). Surgical margins were reported in 6 of 8 dogs; excision was considered complete in 4, narrow in 1 (malignant tumor), and incomplete in 1. Three of the 4 intact dogs were castrated at the time of tumor removal, and none of the dogs had lymph node biopsies performed.

No consistent abnormalities were detected on CBC and chemistry panel in any of the 7 dogs in which they were reported. Three-view thoracic radiographs were performed in 7 of 8 dogs, and none had evidence of metastatic disease. Five of 8 dogs had abdominal imaging performed (abdominal ultrasound with and without abdominal radiographs). Although 2 of 5 were considered to have medial iliac lymph node enlargement, the lymph nodes were not aspirated nor a biopsy performed. Cytologic evaluation of the mammary mass was performed in 4 of 8 dogs. Cytology was suggestive of neoplasia in all 4 dogs, with criteria of malignancy noted in 3 of the 4. Those 3 tumors were deemed benign when reviewed histologically.

Only 1 dog developed possible local recurrence of the mammary-gland tumor. This was the only dog to have been diagnosed with a malignant mammary-gland tumor, and the surgical margins on the original tumor

were considered narrow at the deep margin. Identification of the new tumor was noted approximately 115 days after the original diagnosis. The 2nd tumor was determined to be a mammary adenocarcinoma histologically, but the slide was not available for review. The 2nd surgery was curative as no further tumors were noted in this dog after 610 days follow-up.

At the time of last follow-up, 7 dogs had died, all of causes unrelated to the mammary-gland tumor. One dog was alive with a follow-up of 1,235 days. The median survival time was not reached (range: 175–1,460 days).

Seven of the 8 dogs were from UW and TAMU. Population data from these 2 institutions over a 6.5 year period encompassing the time period of 5 of these cases was used to calculate annual incidence rates of mammary-gland tumor development in female versus male dogs. At these 2 institutions, 25,386 female dogs were seen over the 6.5 year period, and 341 cases of mammary-gland tumors were recorded during that time period for an incidence of 1,343/100,000 over 6.5 years or an annual incidence rate of 207/100,000. Over the same 6.5 year period, 22,905 male dogs were seen at both institutions, and 5 cases of mammary-gland tumor were recorded during that time period for an incidence of 22/100,000 over 6.5 years or an annual incidence rate of 4/100,000. The calculated relative risk of developing mammary-gland tumor is 62 times greater in females than males (95% CI 25–149;  $P < .0001$ ).

ER expression was of strong intensity and occurred in >50% of the neoplastic cells in 6 of 8 dogs (Table 1). PR expression was of slightly lesser intensity and occurred in <50% of the cells in 7 of 8 dogs.

## Discussion

This study illustrates that although rare, mammary-gland tumors can arise in male dogs. The annual incidence rate in female dogs in this study was 207/100,000, which compares favorably to a study that previously reported an annual incidence rate of 199/100,000.<sup>22</sup> In contrast, the incidence rate of mammary-gland tumor development in the male dogs reported here was 4/100,000. Because the incidence of male mammary-gland tumors is extremely low, clinical conclusions regarding their behavior are limited because of their rarity.

We can conclude that this is a disease of older dogs. Furthermore, 3 of 8 dogs were Cocker Spaniels. The population characteristics in this male population mimics those in female dogs where Poodles, Cocker Spaniels and other purebred dogs are over-represented, the median age at diagnosis is 10–11 years, and the majority of tumors are of epithelial origin.<sup>8,23</sup> However, it appears that the incidence of malignant mammary-gland tumors in male dogs is lower than the incidence in female dogs,<sup>2,3</sup> with only 1 of the tumors reported here being malignant. All but 1 of the tumors were incidental findings, emphasizing the importance of thorough palpation of the mammary chains in all dogs, regardless of sex.

As would be expected with the majority of benign tumors, surgery alone provides long-term control and survival in most dogs. In female dogs, metastasis is always of concern in malignant mammary-gland tumors, and approximately 50% of malignant mammary-gland tumors in female dogs will ultimately metastasize to distant sites such as lymph nodes, lungs, liver, and rarely bone.<sup>23</sup> Several prognostic factors have been identified in female dogs to help predict which dogs will eventually suffer from metastatic disease. Some of these include tumor size,<sup>5–7</sup> histologic grade,<sup>2</sup> histologic subtype,<sup>2,5,8</sup> evidence of metastasis at diagnosis,<sup>5–7</sup> and ER and PR expression.<sup>9–12</sup>

All but 1 of the male dogs in this series with strong ER expression in their tumors had benign neoplasms and a good prognosis, as is seen in mammary-gland tumors in female dogs. The 1 malignant neoplasm also had strong and diffuse ER expression. All dogs revealed PR expression in their neoplasms, albeit less intense and less diffuse than for ER. Although the dogs in this study were not routinely reevaluated to document development of metastasis, 7 of 8 dogs died of causes unrelated to their mammary-gland tumors and 1 dog is still alive with a follow-up of 1,235 days. Furthermore, 63% (5 of 8) of the dogs survived longer than 1 year after the diagnosis, with 2 of these dogs surviving longer than 2 years, including the dog with the malignant tumor. All of the male dogs had what are considered favorable prognostic factors in the female, including relatively small tumor sizes, benign or well-differentiated malignant epithelial tumors, no definitive evidence of metastatic disease at diagnosis, and intense ER positivity.

All tumors analyzed were ER+, raising the question of the role of castration, both early in life and at the time of mammary-gland tumor diagnosis. Four of 8 dogs in this study were sexually intact at diagnosis, and 3 of 4 were neutered at the time of mammary-gland tumor surgery. Of the neutered dogs, the date of castration was known in only 1, and that dog was neutered approximately 8 months before diagnosis of his mammary-gland tumor. However, no difference in relative risk of mammary-gland tumor development was noted between the neutered and intact males. Questions regarding the role of sex hormones and the potential for hormonal manipulation as a therapeutic modality in male dogs with mammary-gland tumors cannot be answered based on the small number of dogs and the likelihood that surgery alone is curative in most dogs.

This study is limited by the small number of dogs, but this is a consequence of the rarity of this disease in male dogs. The retrospective nature of the study is also a limitation in that follow-up data was obtained primarily through client and referring veterinarian contact.

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## Footnotes

<sup>a</sup> Target Retrieval System, Dako, Carpinteria, CA

<sup>b</sup> Automated Stainer Model S3400, Dako, Carpinteria, CA

- <sup>c</sup> Nonserum protein block, Dako, Carpinteria, CA  
<sup>d</sup> Estrogen-receptor antibody (Clone NCL-ER), Novocastra Laboratories Ltd., Newcastle upon Tyne, UK  
<sup>e</sup> Progesterone-receptor antibody (Clone PR10A9), Immunotech, Marseille, France  
<sup>f</sup> EnVision+ Anti-rabbit, Dako, Carpinteria, CA  
<sup>g</sup> 3,3 diaminobenzidine, Dako, Carpinteria, CA  
<sup>h</sup> Hematoxylin 2, Richard Allan Scientific, Kalamazoo, MI  
<sup>i</sup> Universal Negative Control+ rabbit serum, Dako, Carpinteria, CA  
<sup>j</sup> Prism v4.0b software, GraphPad Software Inc., San Diego, CA

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