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Evaluation of clinical and pathological characteristics of 155 canines with mammary tumours: a retrospective study

Evaluación de características clínicas y patológicas de 155 caninos con tumores mamarios: un estudio retrospectivo

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RESUMEN

En este estudio se evaluaron en forma retrospectiva las características clínicas y patológicas de 155 perras con tumores mamarios. 55% de los animales con tumores mamarios eran Poodle (83 pacientes). La edad promedio al momento de la excisión del tumor fue de $10,3 \pm 0,2$ años, mientras que el tiempo transcurrido entre la detección del tumor y tratamiento del paciente fue de $308 \pm 38,5$ días. 46 de las 119 perras habían parido al menos una vez y 22 de 59 habían presentado un historial con falsa preñez. Además, 2% de los animales habían presentado tumores de origen vulvar o vaginal. 212 tumores fueron removidos quirúrgicamente y de ellos, 78,3% eran malignos, 12,3% resultaron benignos, 8% eran cambios hiperplásicos y 1,4% eran tumores no clasificados. No hubo asociación significativa entre el tipo histopatológico de los tumores mamarios y edad, raza, ubicación y duración del tumor, estado reproductivo, historial de preñez o pseudopreñez.

Key words: canine, mammary neoplasia, age, breed, histopathology.

Palabras clave: caninos, neoplasia mamaria, edad, raza, histopatología.

INTRODUCTION

Mammary gland is a modified sweat gland which is the second most common site for tumour development after the skin in dogs (Dorn *et al* 1968, Schneider *et al* 1969, Schummer *et al* 1981, Moulton 1990). At 9 to 11 years of age, dogs have maximum risk of developing mammary tumours (MTs) although the risk rises at the age of 6 to 7 years which is defined as the "cancer age" (Schneider 1970, Moulton 1990). Hormonal influences, obesity at a young age and intake of red-meat or home-made diet were determined to increase the risk of tumour development (Schneider *et al* 1969, Briggs 1980, Sonnenschein *et al* 1991, Bruun 1997, Alenza *et al* 1998, Alenza *et al* 2000). Factors like number of pregnancies, history of false pregnancies, regularity of oestrous cycles, number of litters or puppies and their size were found to be unrelated to the development of MTs (Brodey *et al* 1966, Schneider *et al* 1969, Schneider 1970).

Retrospective studies investigating epidemiologic, clinical and pathologic features of MTs in dogs have been previously published (Brodey *et al* 1966, Dorn *et al* 1968, Schneider 1970, Mulligan 1975, Priester 1979, Boldizar *et al* 1992, Hellmen *et al* 1993, Itoh *et al* 2005, Zatloukal *et al* 2005). However, according to the place

where the study was conducted or due to the different classification systems used, features like breeds of dogs at high or low risk and the ratio of benign or malignant tumours varies among the reports. Therefore, the objective of the retrospective study presented here was to identify clinical and pathological characteristics of 155 reviewed canine mammary tumour cases.

MATERIAL AND METHODS

A total of 328 bitches with MTs were clinically examined and surgically treated at the Department of Obstetrics and Gynaecology, between January 1, 2000 and January 1, 2005. Only the animals with histopathologic diagnosis were included in this study ($n = 155$). Breed, age, location of affected mammary glands, tumour size (maximal diameter of the tumour), number of days between the time the tumour was first determined and the time the patient was presented, reproductive history (spaying status, age at spaying, whelping and history of false pregnancy), application of any kind of exogenous hormones and type of surgery (simple mastectomy or radical mastectomy) were obtained from review of medical records or phone calls to the owners. Histopathological examination of the tumours was performed at the Department of Pathology. Histological classification of the samples were performed according to World Health Organization (WHO) classification for mammary tumours of the dog (Misdorp *et al* 1999). However, in addition to WHO classification, malignant mix

tumour was used for the tumours containing both epithelial elements and cartilagenous or osseous components. (Moulton 1990, Helmen *et al* 1993, Funakoshi *et al* 2000, Restucci *et al* 2000). In 2006, the owners were contacted for additional follow-up information.

STATISTICAL METHODS

Statistical analysis were performed using statistical packages for social sciences for Windows 11.5 package program (SPSS 2004). The effects of breed, age, location of the tumour and reproductive status on tumour type were analyzed using Kruskal-Wallis test. The effect of type of surgery on survival time was analyzed with χ^2 test. The correlation between the size of the tumour and survival time was analyzed using the Mann-Whitney U test. Survival time was defined as the time from surgery to death, was analyzed using Kaplan-Meier method and were compared using the log-rank test between dogs grouped according to factors as follows; age (< 10 vs \geq 10 years), breed (Poodle vs other breeds), reproductive status (spayed vs intact), number of tumours (single vs multiple), maximal diameter of tumours (< 5 vs \geq 5 cm), type of surgery (simple mastectomy vs radical mastectomy), histological diagnosis (benign vs malignant), (< 6 vs \geq 6 months), the use of exogenous hormones (yes vs no), whelping (yes vs no) and history of pseudopregnancy (yes vs no).

RESULTS

In the present study, it was determined that some of the information was not recorded or could not be followed-up by telephone.

As seen in table 1, 22 different breeds (excluding mixed breed dogs) were represented in 155 dogs and Poodle was the most commonly affected breed with 83 cases determined in this study.

The mean age of 150 dogs at the time of examination was 10.3 ± 0.2 years, with a range of 4 to 17 years (figure 1). However, age at detection of the tumour was 9.37 ± 0.27 years with a range of 3 to 15 years in 93 dogs. Duration of tumour growth was recorded in 91 dogs which was between 2 and 1,460 days with an average of 308 ± 38.5 days. The mean age of dogs with benign tumours at the time of examination was 9.38 ± 0.48 years while for those with malignant tumours it was 10.15 ± 0.23 years. Dysplasia or hyperplasia was diagnosed at the mean age of 9.6 ± 0.81 years. However, no significant difference ($P < 0.05$) was found between the ages of animals diagnosed with dysplasia/hyperplasia or benign or malignant tumours.

Location of the tumour was recorded in 88 cases. The mammary glands involved by 133 tumours were as follows: thoracal (22.5%), abdominal (30.1%) and inguinal (47.4%). The ratio of malignant tumours in thoracal, abdominal and inguinal mammary glands were 89%, 70% and 79%, respectively. The size of 82 tumours varied from 0.5 cm

to 18.0 cm with an average of 3.58 ± 0.34 cm. Malignant tumours ($n = 74$, size = 5.5 ± 0.47 cm) were larger than benign tumours ($n = 8$, size = 3.07 ± 1.03 cm) without statistical significance ($P < 0.05$).

All the dogs with MTs were female and 92 of 121 dogs (76%) were sexually intact at the time of examination. Regarding the spayed bitches (24%), spaying was performed in 1 animal at 9 months old; in 3 at 2 years; in 1 each at 4, 5, 7, 12 and 13 years; in 4 at 6; in 2 at 8; 3 each at 9 and 10 years and in 8 animals at unknown time. The owners of two animals, indicated that one of the ovaries was not removed at the time of spaying. Fourty-six out of the 119 (38%) dogs had whelped at least once in their life-time. Out of the 82 dogs, six had a history of hormonal treatment in which steroid hormones were used in two dogs for the treatment of skin diseases and oestrogen was used in one bitch to terminate pregnancy. In three dogs the reason of the use was not identified. Pseudopregnancy was recorded in 22 of 59 bitches. Three out of 155 animals (1.9%) with mammary tumours also had vulvar (1 dog) and vaginal (2 dogs) tumours of myoma, fibropapilloma and leiomyoma.

Two hundred and twelve tumours were surgically removed since 57 out of the 155 dogs were presented with more than one tumour. Of the 212 tumours, 78.3% were malignant tumours, 12.3% were benign, 8.0% were hyperplastic changes and 1.4% were unclassified tumours.

Follow-up information was obtained from the owners of 65 dogs in which 32 died because of related, unrelated or unknown causes. Of the 32 dogs, death was unrelated with mammary tumours (pyometra, hypothyroidism, ingestion of foreign body, paresis, nasal tumour, fall and lethargy) in seven animals, recurrence in two and respiratory disease in seven. Euthanasia was reported in four animals due to recurrence and in two dogs due to undetermined reasons. The cause of death of the remaining 10 animals was not reported. No necropsy was performed or reported in any animal. The average postmastectomy survival time was 331 ± 64 days for 32 dogs. Median survivals for 32 dogs with malignant and benign tumours were 304 and 575 days, respectively. The survival rates of animals that had radical mastectomy ($n = 20$) were higher than those in dogs that had simple mastectomy ($n = 38$) although there were no significant differences ($P < 0.05$).

No significant relationship ($P < 0.05$) was found between the histologic diagnosis of the mammary tumours and breed, age, duration, location or size of the tumour, reproductive history including spaying status, pregnancy or pseudopregnancy and application of exogenous hormones.

DISCUSSION

In the present study, a total of 155 bitches with MTs that were surgically treated at the Department of Obstetrics and Gynaecology were evaluated retrospectively to explore

Table 1. Breed distribution of 155 dogs with mammary tumours.
Distribución de razas de 155 perras con tumores mamarios.

Breed	Number of dogs	Number of tumours	Number of dogs with benign tumours	Number of dogs with malignant tumours	Number of dogs with hyperplasias/dysplasias	Number of dogs with unclassified tumours
Poodle	83	112	11	93	8	0
Cocker Spaniel	11	17	1	14	2	0
Mixed breed	10	12	2	8	1	1
Boxer	6	8	1	7	0	0
Miniature Pinscher	5	9	1	8	0	0
German Shepherd	5	7	0	7	0	0
Rough Collie	5	5	0	4	0	1
Anatolian Shepherd dog	4	6	1	4	1	0
Pekingese	4	9	2	4	3	0
Great Dane	1	1	0	1	0	0
Miniature Spitz	1	1	1	0	0	0
Golden Retriever	1	1	1	0	0	0
Beagle	1	2	0	2	0	0
Samoyed	1	1	0	1	0	0
Caucasian Sheep dog	1	1	0	1	0	0
Dachshund	1	1	0	1	0	0
Irish Setter	3	3	1	2	0	0
Pointer	2	2	0	2	0	0
Doberman Pinscher	1	1	0	1	0	0
English Setter	1	1	0	1	0	0
Dalmatian	1	4	2	1	1	0
Chihuahua	1	1	0	1	0	0
Tibetan Terrier	1	1	0	1	0	0
Unknown	5	6	2	2	1	1
Total	155	212	26	166	17	3

clinicopathologic characteristics of MTs in female dogs. Despite the fact that 328 female dogs with MTs were treated between 2000 and 2005, histopathologic identification could not be made in all cases due to the owners' financial constraints.

Mammary tumours were determined in 22 different purebred dogs. Poodle was the most commonly affected breed although sporting dogs including Pointers, Retrievers, English Setters and Spaniels were reported to have a higher frequency (Priester 1979, Moulton 1990). This may be related to the fact that small or miniature dogs, especially poodles, are the dominant house-hold pets in this region compared to medium or large sized dogs. Therefore, we agree with the belief that breed predisposition varies due to the pet population (Alenza *et al* 2000).

Mean age at detection of the tumour was 9.37 years with a range of 3-to-15 years. However, duration of the tumour before presentation was between 2 and 1460 days with an average of 308 days which means that the dogs were brought approximately a year after the detection of

the mass by the owner. Because of this reason the mean age at the time of examination was 10.3 years (range 4-to-17) which is in accordance with the ages reported in several studies (Schneider 1969, Boldizar *et al* 1992, Zatloukal *et al* 2005).

Both in our study and in the study by Chang *et al* (2005), dogs were examined and treated more or less a year after the detection of the mass. It is our opinion that some private practitioners prefer to wait until the tumour becomes big in size before referring the patient or establishing a treatment plan. In addition, we also believe that the owners disregard the disease or postpone the examination if no signs of pain or suffering are observed in their animal. This hypothesis was supported by a study (Alenza *et al* 2001) in which dogs with inflammatory carcinoma suffering from generalized weakness, signs of pain and inflammatory changes, were examined and treated approximately 55 days after the perception of the clinical signs by the owner.

Benign tumours occurred one to two years earlier than malignant tumours which coincides with the findings of

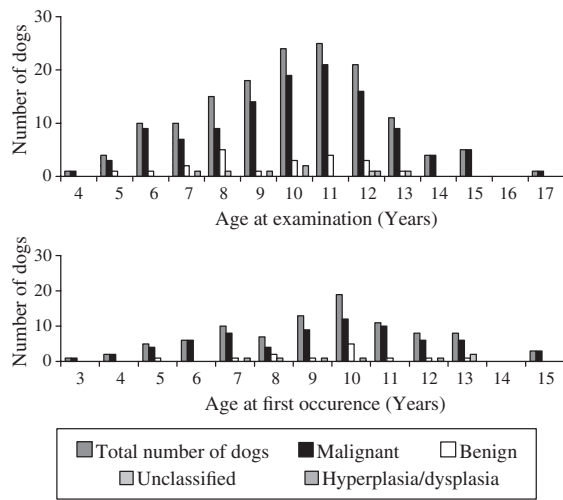


Figure 1. Age distribution of dogs with mammary tumours at surgery and at first occurrence.

Distribución de la edad de perras con tumores mamarios, en cirugía y en primera ocurrencia.

previous studies (Moulton 1990, Zatloukal *et al* 2005). In two reports (Miller *et al* 2001, Zatloukal *et al* 2005) the mean age of dogs with dysplastic or hyperplastic changes were determined to be 6.1 and 8.3 years, respectively, which contrasts with the mean age found in the present study (9.6 years). In our opinion, this could be related to the delayed presentation of the patients because of the previously mentioned reasons. The mean age of the dogs with malignant tumours was 10 years which is in correspondance with the mean age of dogs with malignant mammary tumours in the other studies (Moulton 1990, Zatloukal *et al* 2005). Growing age is highly related with malignancy due to accumulation of tumourogenous factors leading to malignant tumours by advancing age (Zatloukal *et al* 2005).

Tumour development was most commonly determined in inguinal mammary glands which is in accordance with previous studies (Mulligan 1975, Moulton *et al* 1986, Moulton 1990, Miller *et al* 2001, Vural and Aydın 2001). The reason of the increased frequency in the last two glands is unknown, however, several explanations such as presence of larger mass of tissue, or greater proliferative change in response to oestrogen in the most caudal glands have been suggested (Moulton *et al* 1986, Moulton 1990). Furthermore, hyperplastic nodules which occur most commonly in the last two glands, are considered the beginning stages of tumourogenesis (Moulton *et al* 1986, Hellmen 1996).

Reproductive history of the bitches reported here was similar to those documented elsewhere (Brodey *et al* 1966, Schneider *et al* 1969, Priester 1979). Most bitches were sexually intact which may suggest that the risk of tumour

Table 2. Histologic types and number of tumours presented between 2000 and 2005.

Tipos histológicos y número de tumores presentados entre los años 2000 y 2005.

Number of tumours	Histologic diagnosis	%
166	Malignant Tumours	78.30
60	Simple carcinoma	28.30
32	Complex carcinoma	15.09
25	Malignant mixed tumour	15.06
23	Carcinosarcoma	13.85
12	Osteosarcoma	5.66
5	Noninfiltrating (in situ) carcinoma	2.36
4	Other sarcomas	1.89
3	Fibrosarcoma	1.42
1	Spindle cell carcinoma	0.47
1	Squamous cell carcinoma	0.47
26	Benign Tumours	12.27
10	Benign mixed tumour	4.72
7	Adenoma	3.30
6	Fibroadenoma	2.83
3	Duct papilloma	1.42
3	Unclassified Tumours	1.41
1	Mast cell tumour	0.47
1	Lipoma	0.47
1	Osteochondrom	0.47
17	Hyperplasias/Dysplasias	8.02
9	Duct ectasia	4.25
6	Adenosis	2.83
1	Endrinopathy	0.47
1	Osteoma	0.47

development may be higher in intact bitches than in spayed bitches (Frye *et al* 1967). One of the most interesting findings in the present study was, two animals with ovarian remnant syndrome that had mammary tumours, which is not indicated previously. No significant correlation was found between the development of MTs and pregnancy or pseudopregnancy that corresponds well with the studies by Brodey *et al* (1966) and Schneider *et al* (1969). Although, the incidence of mammary gland tumours may increase when progestagens and oestrogens are used at high dosages or at the wrong time or at prolonged administration, in this study, the use of progestagens was not recorded in any animals (Briggs 1980, Van Os *et al* 1981, Bruun 1997). This is probably related with less attraction of the private practitioners to the use of hormonal contraception in small animal practice in this region.



Figure 2. A 7 year-old, sexually intact, Chihuahua bitch presented with a small mass in the inguinal mammary gland. The mass was histopathologically diagnosed as simple carcinoma.

Perra Chihuahua de 7 años de edad, sexualmente intacta, presentando una pequeña masa en la glándula mamaria inguinal. La masa fue histopatológicamente diagnosticada como carcinoma simple.

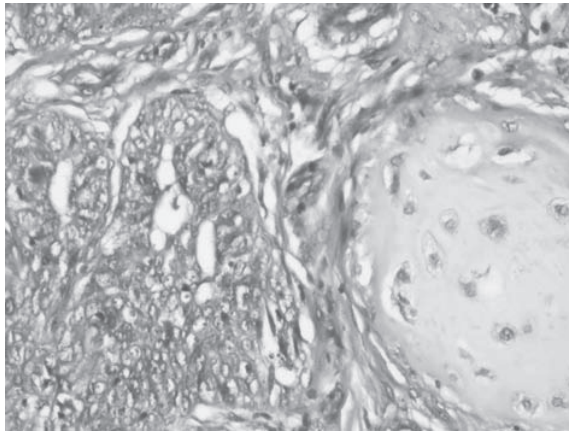


Figure 4. Malignant mix tumour in the left inguinal mammary gland of a 4.5 year-old, sexually intact, German shepherd bitch. Atypical gland epithelial cells located adjacent to cartilagenous component is shown. (Haematoxylin and eosin X 400).

Tumor mixto maligno en la glándula mamaria izquierda de una perra pastor alemán de 4,5 años de edad, sexualmente intacta. Se observan células epiteliales glandulares atípicas ubicadas en forma adyacente al componente cartilagenoso.

The aims of determining the survival time following the surgery and the effects of investigated variables such as tumour size or type of surgery on survival failed because of several reasons. First of all, follow-up information was obtained from 65 of 155 owners which was evaluated as a small sample number to make a clear statement. In addition to this, in 7 of 31 dogs, the cause of death was unrelated to MTs like pyometra, hypothyroidism or ingestion of foreign body. Moreover, it was clearly observed that after the surgical removal of the tumours, the animals were



Figure 3. An 8 year-old, sexually intact, Terrier bitch was presented with a 4 months history of a large mass as big as a baby head in the inguinal mammary gland. The dog was euthanized due to the inoperable size of the mass. Histopathological diagnosis of the mass was not determined because neither a necropsy nor a biopsy has been permitted.

Perra Terrier de 8 años de edad, sexualmente intacta, presentando un historial de 4 meses con una masa tan grande como la cabeza de un bebé en la glándula mamaria inguinal. Se le aplicó eutanasia debido al tamaño inoperable de esta masa. El diagnóstico histopatológico de la masa no fue determinado, ya que ni la necropsia ni la biopsia fueron permitidas.

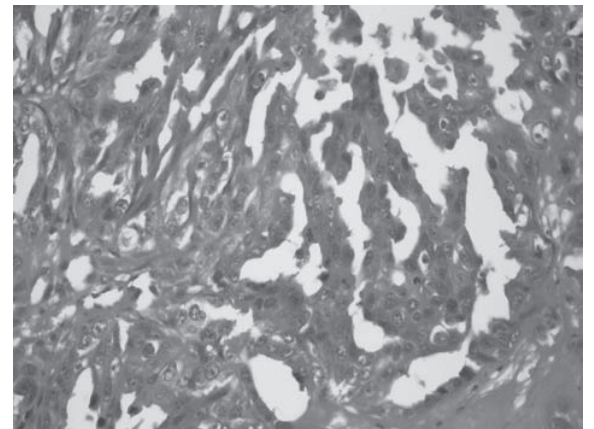


Figure 5. Simple carcinoma (tubulopapillary carcinoma) in a 9 year-old, sexually intact, mixed-breed dog. Various sized tubular structures and branching tubules are demonstrated. (Haematoxylin and eosin X 400).

Carcinoma simple (carcinoma tubulopapilar) en una perra de raza mixta de 9 años de edad, sexualmente intacta. Se observan estructuras tubulares de varios tamaños y túbulos ramificados (Hematoxilina y eosina X 400).

examined in private clinics for subsequent diseases which prevented us to follow-up the patients and to perform necropsies on them. The data of survival time found in the present study should be considered only descriptive because of the low sample number and of the low power of the statistical analyses.

Histopathological diagnosis of MTs is crucial in prediction of tumour behaviour after surgical excision. Moreover, histopathologic typing of the tumour is also important in establishing a post-operative chemotherapy plan to increase the survival time following the surgery since several protocols have been used with success in dogs (Karayannopoulou *et al* 2001). Various classification systems (Hampe and Misdorp 1974, Gilbertson *et al* 1983, Misdorp *et al* 1999) have been developed to estimate the prognosis of the disease. However, because of the lack of a standart criteria to differentiate benign from malignant tumours, the incidence of malignant tumours varies widely from 39 to 91 per cent according to different reports (Priester 1979, Nerurkar *et al* 1989, Hellmen *et al* 1993, Vural and Aydın 2001, Martins *et al* 2002, Itoh *et al* 2005, Zatloukal *et al* 2005). In the current study, the histologic ratio of malignant to benign tumours was approximately 7:3 which is in accordance with those determined in most studies (Priester 1979, Nerurkar *et al* 1989, Hellmen *et al* 1993, Vural and Aydın 2001, Martins *et al* 2002, Itoh *et al* 2005) whereas, in contrast to Misdorp *et al* (1999). This interesting regional difference may be due to a) the duration of the growth before the diagnosis; b) the age of the dogs; and c) high prevalence of unspayed animals. In five dogs presented with more than one tumour, the histological diagnosis of each mammary mass was determined to be different. This means that a dog presented with multiple mammary tumours may have benign and malignant tumours at the same time, which also confirms the importance of histological examination.

The average time from the detection of the tumour to presentation was approximately 308 days which is a sufficient time for transitions between dysplasias, benign tumours and carcinomas. According to Hellmen (1996), hyperplastic and preneoplastic nodules exist in the mammary gland which may become tumourous lesions by time. And also, dysplastic or hyperplastic changes in the mammary glands are considered preneoplastic that are the initial stages in the multi-step process of tumourogenesis (Schneider *et al* 1969, Hellmen 1996). The low incidence of dysplastic or hyperplastic changes compared to benign and malignant tumours is in accordance with previous studies which may also be associated with the time of consultation that seems to occur late in progress of the disease (Vural and Aydın 2001, Martins *et al* 2002, Zatloukal *et al* 2005).

Finally, this study demonstrated that in the bitch, mammary tumours occur most commonly in the last two glands of small breed dogs at the age of 10 to 11 years and the nature of the tumours is histologically malignant.

SUMMARY

In the present study, clinical and pathologic features of 155 bitches with mammary tumours were evaluated retrospectively. Fifty-five per cent of the animals with mammary tumours were Poodles (83 patients).

Mean age at the time of tumour excision was 10.3 ± 0.2 years and days between the time the tumour was first determined and the time the dog was presented were 308 ± 38.5 days. Forty-six of the 119 dogs whelped at least once and 22 of 59 dogs had a history of false pregnancy. Two per cent of the animals also had tumours of vulvar and vaginal origine. Two-hundred and twelve tumours were surgically removed and out of the 212 tumours, 78.3% were malignant, 12.3% were benign, 8.0% were hyperplastic changes and 1.4% were unclassified tumours. No significant association was found between the histopathological type of mammary tumours and age, breed, location and duration of the tumour, reproductive status, history of pregnancy or pseudopregnancy.

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