

# A Study on the Relationship Between Tumor Size, Tumor Grade and Lymph Node Involvement in Canine Mammary Cancer: Simulation of Tumor Behavior in Human Breast Cancer

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**Background:** In the last two decades, canine mammary cancer has played an essential role in human breast cancer research. There are various similarities between biological and clinical features of canine breast cancer and female breast cancer in many cases. Clinical studies and evaluation of prognostic factors in canine mammary cancer can increase reliability in generalizing results to human cancers. This study was performed in the direction of comparative oncology.

**Methods:** We collected clinicopathological data of an invasive type of canine mammary carcinoma from clinical records and pathology reports. Age, tumor laterality, tumor size, lymph node status, and tumor grade were recorded, and the relationships between the parameters were evaluated using linear regression analysis.

**Results:** Ninety-seven patients were included in the study, and the mean age was  $10.06 \pm 2.73$  years. The left mammary gland was involved in 51% of cases, and pT2 was the most common tumor size. Lymph nodes were involved in 27% of patients, and 43% of tumors were grade I. Statistical analysis showed no relationship between tumor size and laterality with other clinicopathological features. However, there was a statistically significant relationship between tumor size and tumor grade, and lymph node status. As the tumor size increased, tumor grade and the risk of lymph node involvement raised.

**Conclusion:** Similar results of this study to breast cancer in women show that canine mammary carcinoma is a suitable model in comparative oncology research. Dogs live shorter than humans so that researchers can get the results of treatment and perform survival rate assessments faster in clinical trials. By considering ethical principles, dogs with breast cancer may replace phases I and II of human clinical trials in some cancer types soon.

**Keywords:** Canine Mammary Carcinoma, Tumor Size, Tumor Grade, Lymph Node Status, Comparative Oncology



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## INTRODUCTION:

In recent years, canine mammary cancer has become the focus of cancer researchers. Many studies show that dogs' spontaneous mammary gland tumors are an excellent model for human breast cancer research. Clinical and biological findings of canine mammary cancer are similar to human breast cancer in many ways, and today it has a special place in comparative oncology studies (1). Human breast cancer researchers have described the relationship between tumor size and lymph node involvement for many years (2). Tumor size in human breast cancer is a component of TNM staging and is classified as T1-T3 (3). In canine mammary cancer, tumor size is also one of the critical components of TNM staging. The only difference with human breast cancer is related to the size of T1 and T2, as T1 is related to 3 cm tumors and T2 refers to 3-5 cm tumors (4). However, in recent studies, similar to human breast cancer, tumor diameter of 2 cm or less has been designated as T1 (5).

In canine mammary cancer, similar to human breast cancer, tumor size is considered a prognostic factor. Studies show that tumor size in canine mammary cancer is associated with patients' survival rate (6). Positive lymph nodes also reduce the overall survival rate (7). Due to the increase in companion animals' population, comparative oncology studies in Iran have been developed (8). In this study, the relationship between canine mammary tumor size and lymph node status, and some clinical and pathological features has been determined. A comparative aspect of oncology has also been investigated.

## METHODS:

This is a retrospective study. The clinicopathological data of 97 canine mammary tumors were examined. From the clinical record and pathology report of patients, parameters including age, tumor size, tumor laterality (position of a tumor on the right or left side of

the body), lymph node status, tumor grade, and the type of surgical procedure were extracted. Tumor size (pT) was classified as T1 < 2 cm, T2 = 2-4.9 cm, and T3 ≥ 5 (5). The status of lymph nodes (pN) was recorded as negative (N0) or positive (N1). Tumor grade was recorded as G1, G2, and G3 for each patient.

For initial data analysis and descriptive statistics, central and dispersion indicators (including the mean, median, mode, standard deviation, variance, minimum, and maximum) were evaluated. Also, linear regression analysis was performed to analyze the data using the latest edition of GraphPad online software. A P-value less than 0.05 was considered statistically significant.

## RESULTS:

### A. Description of patients' condition

In this study, we assessed the clinicopathological data of 97 cases of the invasive type of canine mammary carcinoma. The minimum age of patients was five years, and the maximum was 15 (with a range of 10 years), and the mean and standard deviation of the age was  $10.06 \pm 2.73$  years (**Table 1**).

More than 50% of tumors were on the left side, and most surgical procedures were simple mastectomy. The mean tumor size was  $1.77 \pm 0.68$ . The T2 group had the highest, and the T3 group had the lowest frequency. About three-quarters of patients had negative lymph nodes. Grade I and grade III had the highest and lowest frequencies, respectively (**Table 1**).

### B. Relationship between patients' age with clinical and pathological parameters

There was no relationship between age and lymphatic involvement ( $P = 0.653$ ), although there was a slight tendency to an increased risk of involvement with age (Equation:  $Y = 0.007555 * X + 0.1920$ ) (**Figure 1A**). There was a weak and inverse relationship between patients' age and tumor grade (**Figure 1B**), which was not statistically significant ( $P = 0.286$ ;  $Y = -0.03015 * X$

**Table 1. Clinicopathological results of canine mammary carcinoma, invasive type in the present study**

Parameter	Category	Frequency & Percentage
Age	5-7 Y/O	21 (21.7%)
	8-11 Y/O	43 (44.3%)
	≥ 12Y/O	33 (34.0%)
Tumor laterality	Right	47 (48.5%)
	Left	50 (51.5%)
Type of surgery	Simple mastectomy	51 (52.5%)
	Regional mastectomy	33 (34.0%)
	Radical mastectomy	13 (13.4%)
pT status (tumor size category)	pT1	36 (37.1%)
	pT2	47 (48.5%)
	pT3	14 (14.4%)
pN status (lymph node category)	pN0	71 (73.2%)
	pN1	26 (26.8%)
Tumor grade	G1	42 (43.3%)
	G2	37 (38.1%)
	G3	18 (18.5%)

+ 2.056). There was a similarly weak and inverse relationship between patients' age and tumor size (**Figure 1C**) that did not reach a statistically significant level ( $P = 0.311$ ;  $Y = -0.02612 * X + 2.036$ ).

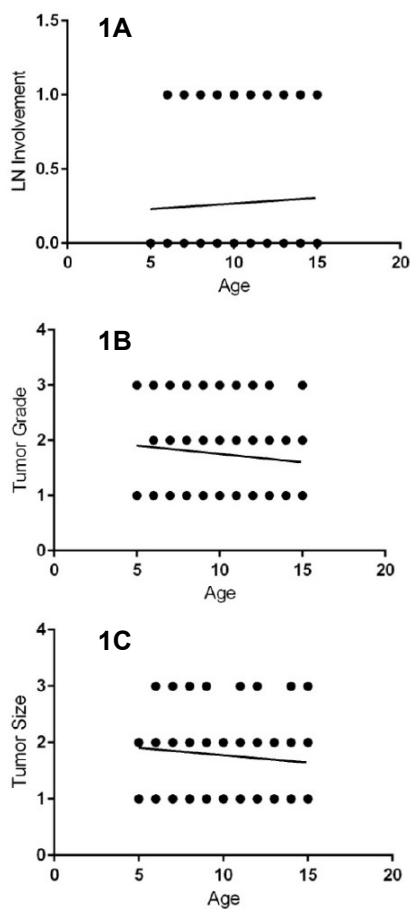
### **C. Relationship between tumor laterality and tumor size, lymph node involvement, and tumor grade**

There was no statistically significant relationship between laterality and tumor size ( $P = 0.324$ ) and the corresponding equation was  $Y = -0.1379 * X + 1.840$  (**Figure 2A**). In addition, there was no statistically significant relationship between laterality and lymph node involvement ( $P = 0.856$ ) when the relevant equation was obtained as  $Y = 0.01660 * X + 0.2600$  (**Figure 2B**). There was no statistically significant relationship between laterality and tumor grade ( $P = 0.713$ ), with a corresponding equation of  $Y = -0.05660 * X + 1.780$

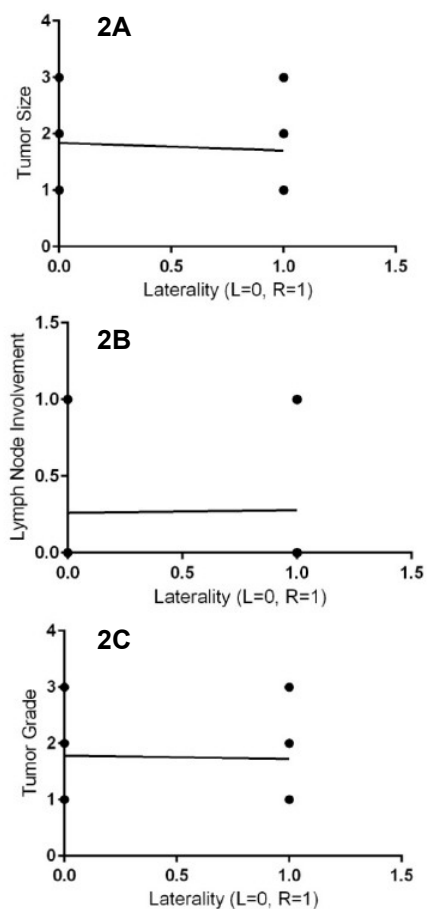
(**Figure 2C**).

### **D. Relationships between tumor size, tumor grade, and lymph node:**

Based on the obtained equation ( $Y = 0.2865 * X - 0.2400$ ), there was a statistically significant relationship between tumor size and lymph node involvement ( $P < 0.0001$ ) (**Figure 3A**). On the other hand, there was a statistically significant direct relationship between tumor size and tumor grade, meaning that the larger the tumor, the higher the tumor grade ( $P < 0.001$ ; equation  $Y = 0.5011 * X + 0.8639$ ) (**Figure 3B**). There was a statistically significant direct relationship between tumor grade and lymph node involvement ( $P < 0.0001$ ), meaning that lymph nodes were more involved in grade 3 than grade 2, and grade 2 than grade 1 (equation  $Y = 0.3225 * X - 0.2971$ ) (**Figure 3C**).



**Figure 1.** Relationship between patients' age and clinicopathological parameters.)



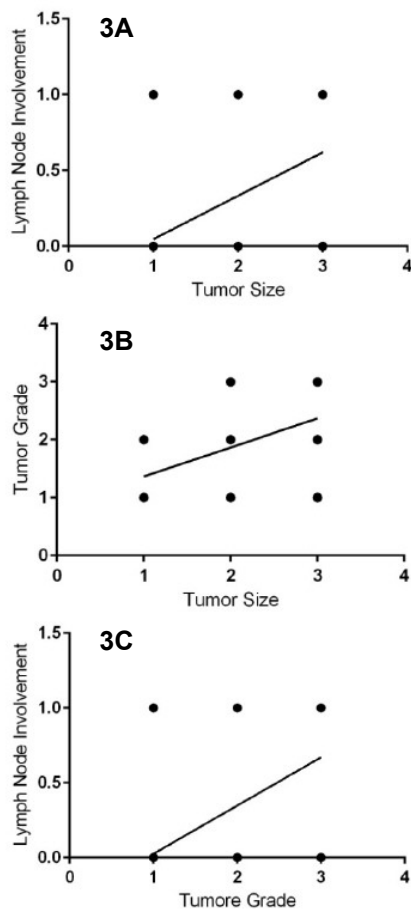
**Figure 2.** Relationship between tumor laterality and clinicopathological parameters

### DISCUSSION:

Based on the findings of the present study, there was a statistical relationship between tumor size, the histological grade of the tumor, and lymph node involvement. In human breast cancer, tumor size plays an essential role in the patients' prognosis and determining treatment strategy (9-10). However, conflicting studies are available that do not find a relationship between tumor size and metastasis (11). There is ample scientific evidence that in canine mammary cancer, similar to breast cancer in women, larger tumor size is associated with

poor clinical and pathological features of the patient (12-13). Increasing tumor size causes an increasingly heterogeneous population in tumor cells and, as a result, with increasing genetic and molecular changes in cancer cells, their invasiveness, and metastasis increase (14-16). In our study, tumor size was significantly associated with lymph node involvement and the tumor's histological grade. As the tumor size increased, the tumor grade and the risk of lymph node involvement increased.

In canine mammary cancer, the regional lymph nodes



**Figure 3.** Correlations between tumor size, tumor grade, and lymph node involvement members of the IRCNNC.

are the first site of metastasis. The malignant breast cells reach the regional lymph nodes through the lymphatic drainage system; secondary foci are formed in them, and, finally, distant metastases occur (17). The prognostic value of lymph node status in canine mammary cancer is similar to that of female breast cancer (18). In women with breast cancer, the number of lymph nodes involved in the axilla has an essential value in the prognosis of the disease. Although some studies show that the involvement of more than one lymph node can increase the risk of distant metastasis, the clinical value

of the number of lymph nodes involved is still unclear (19). Studies also show that in canine mammary carcinomas, changes in genetic and molecular profiles affect the strength of lymph node metastasis, which, in this regard, has similarities to female breast cancer (20). The grading of canine mammary cancer is quite similar to human breast cancer, and, in terms of prognosis, the risk of metastasis increases in higher grades (21). The results of our study on 97 canine patients showed a statistically significant relationship between tumor size and grade and between the histological grade of tumor and lymph node involvement. Therefore, our results are in line with partially-similar studies. On the other hand, in this study, no relationship was found between age and tumor laterality with clinicopathological features. This may have been either influenced by sample size or related to the biological factors, which necessitates extra studies in this field.

In recent years, the role of canine mammary cancer in comparative oncology studies has become more prominent. The reasons for this are as follows: on the one hand, common risk factors and environmental factors between canine and human breast cancer have many similarities (20). On the other hand, the biology and clinical behavior of breast tumors in dogs are very similar to those of humans (21). Therefore, researchers believe that Comparative oncology can help treat canine and human cancers more effectively (21-24). On the NIH/NCI website, clinical trials registered in comparative oncology are available on February 19, 2021.

### CONCLUSION:

Canine mammary tumors are an excellent model for cancer research because, unlike mouse models in which tumors are induced or caused by cell lines, canine mammary cancer is similar to spontaneous human breast cancer and is very similar in invasion and metastasis to human cases. Cooperation of veterinary oncology with human oncology researchers could offer the sci-

entific community a brilliant future cancer study.

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