

## Clinicopathological Survey of 101 Canine Mammary Gland Tumors: Differences between Small-Breed Dogs and Others

Teruo ITOH<sup>1)</sup>, Kazuyuki UCHIDA<sup>2)\*</sup>, Kenichi ISHIKAWA<sup>1)</sup>, Kiyotaka KUSHIMA<sup>1)</sup>, Eiko KUSHIMA<sup>1)</sup>, Hiroyoshi TAMADA<sup>1)</sup>, Takashi MORITAKE<sup>1)</sup>, Hiroyuki NAKAO<sup>3)</sup> and Hiroki SHII<sup>1)</sup>

<sup>1)</sup>Division of Animal Medical Research, Hassen-kai, 2-27 Onozaki, Saito-shi, Miyazaki 881-0012, <sup>2)</sup>Department of Veterinary Pathology, Faculty of Agriculture, Miyazaki University, Miyazaki 889-2155 and <sup>3)</sup>Department of Public Health, Miyazaki Medical College, Miyazaki University, Miyazaki, 889-1692, Japan

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**ABSTRACT.** Clinicopathological features of mammary gland tumors (MGTs) in 101 dogs were evaluated retrospectively. The incidence of histological malignancy in 60 small- and 41 other-breed dogs were 25% and 58.5%, respectively. In 82 epithelial MGTs, small-sized tumors (< 3 cm) or non-invasive tumors were predominant in small breeds. In multivariate survival analysis, small breed ( $p=0.048$ ) and lower stage of tumor cell invasion ( $p=0.006$ ) were significantly associated with longer survival time. These results suggest that the incidence of histological or biological malignancy in MGTs is lower in small-breed dogs than in others.

**KEY WORDS:** canine, clinicopathological survey, mammary gland tumor.

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Mammary gland tumors (MGTs) are the most common neoplasms occurring in female dogs [2]. Although approximately 50% of MGTs are malignant [3, 7], the incidence of malignancy varies among the reports, ranging from 34% [10] to 93% [4]. As a cause of this wide range, the lack of uniform histological criteria to assess malignancy has been pointed out [3, 12], which also influences the prognostic data on malignant MGTs [3].

In most previous studies from foreign countries, the 2-year survival rates of dogs with malignant MGTs after surgery were less than 50% [1, 5, 6, 9, 11], whereas the rate reported in Japan was more than 80% [13]. However, it is unclear whether this difference is due to the histological criteria used or the epidemiological feature in Japan where small-breed dogs are predominant. The purpose of this study is to evaluate clinical outcomes of both benign and malignant canine MGTs with concern to the differences between small-breed dogs and others.

One hundred and one dogs with MGTs, treated surgically at 7 private practices in Miyazaki prefecture from 1997 to 2002, were evaluated retrospectively. Age, breed, body weight, gender, the time of spaying, number of tumors, size of tumors, lymph node status, radiographic evidence of distant metastasis, histopathological features, treatments, post-operative outcome, and cause of death were obtained from each medical record or phone calls to the owners. Histopathological diagnosis was made at the Department of Veterinary Pathology in Miyazaki University. In multiple tumors, the most malignant tumor was used for the grouping. All epithelial tumors were classified according to invasion of tumor cells as follows: stage 0; no stromal invasion, stage I; stromal invasion without vascular invasion, and

stage II; vascular invasion. Histopathologically, 62 (61.4%) were diagnosed as benign MGTs consisting of 26 complex adenomas, 18 benign mixed tumors, and 18 adenomas. Other 39 (38.6%) consisted of 25 adenocarcinomas, 7 complex adenocarcinomas, 2 anaplastic carcinomas, 2 carcinomas in mixed tumor, 2 sarcomas, and 1 spindle cell carcinoma. Tumor-related death was confirmed in 15 of 39 dogs (38.5%) with malignant MGTs during the study periods, whereas neither distant metastasis nor recurrence at the primary site had been confirmed in dogs with benign MGTs.

Of all 101 dogs, 60 (59.4%) were regarded as small-breed dogs with distribution as follows: 28 Malteses, 8 Yorkshire terriers, 6 Shih-Tzues, 5 Miniature dachshounds, 3 Miniature pinschers, 3 Pomeranians, 2 Toy poodles, 2 Chihuahuas and 3 mixed toy dogs less than 4 kg body weight. Mean age of these dogs was  $10.0 \pm 3.0$  years old (range: 2-15) and mean body weight was  $3.8 \pm 2.0$  kg (range: 1.8-5.8). Other 41 dogs consisted of 4 Siberian huskys, 4 Shibas, 3 Golden retrievers, 2 Shetland sheep dogs, 13 mixed-breed dogs and 15 various pure-breed dogs. Mean age of these 41 dogs was  $9.7 \pm 3.5$  years old (range: 5-16) and mean body weight was  $18.9 \pm 11.4$  kg (range: 7.6-34.2). All 101 dogs were female: 80 were intact (small breed: 53, others: 27) and 21 were spayed (small breed: 7, others: 14).

Analysis of survival time defined as the time from surgery to death was performed in dogs with epithelial MGTs. Three cases were excluded because follow-up was less than 1 year, and the remaining cases of 78 epithelial tumors or 36 carcinomas were analyzed. Survival curves were estimated using Kaplan-Meier method, and were compared using the log-rank test between dogs grouped according to factors as follows; breed (small breed vs others), age (< 10 vs  $\geq 10$  yrs), reproductive status (intact vs spayed), number of tumors (single vs multiple), maximal diameter of tumors (< 3cm vs  $\geq 3$ cm), type of surgery (partial vs uni- or bilateral mastectomy), histological diagnosis (benign vs malignant)

\*CORRESPONDENCE TO: UCHIDA, K., Department of Veterinary Pathology, Faculty of Agriculture, Miyazaki University, Miyazaki 889-2155, Japan.

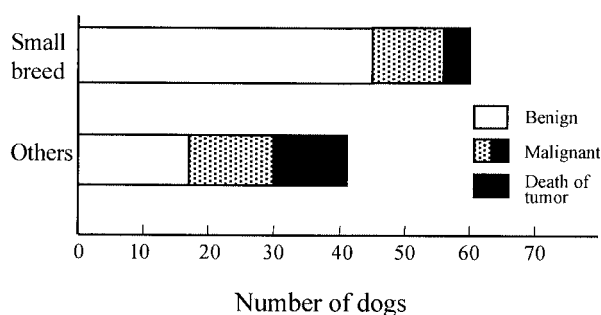


Fig. 1. Numbers of cases histologically diagnosed as benign and malignant, and cases that died of tumor in small-breed dogs and others.

and histological stage. Lymph node involvement ( $n=5$ ), distant metastasis at surgery ( $n=1$ ), and postoperative chemotherapy ( $n=2$ ) were not evaluated because of a small number of cases. Multivariate analysis including factors significantly associated with survival by the log-rank test was performed using forward Cox regression procedure. Dogs that died of MGTs ( $n=12$ ) or unknown cause ( $n=2$ ) were considered completed events. Dogs were censored in the survival analysis for the following reasons; lost to follow-up, death by other than MGTs, or alive at the end of the study periods. A value of  $p<0.05$  was considered significant.

The incidence of malignancy was different between small-breed dogs and others (Fig. 1). In small-breed dogs, 15 (25.0%) were histologically malignant and only 4 (6.7%) had died of MGTs, whereas in other dogs, 24 (58.5%) were diagnosed as malignant and 11 (26.8%) had died of MGTs. The marked differences in histopathological evidence or clinical outcome between the groups were noted in the epi-

thelial tumors (Table 1). In small-breed dogs, non-invasive type (stage 0) was predominant with a low mortality rate even in the stage II cases. Whereas in other dogs, invasive-type (stage I to II) was predominant in which most cases of stage II had died of MGTs. In these 81 cases of epithelial tumors, the rates of small-sized tumor in small-breed dogs and others were 77.6% and 50.0%, respectively. The lower mortality rate in small-sized tumor cases was noted in both breed groups (Table 2). As shown in Table 3, more cases had received uni- or bilateral mastectomy in small-breed dogs (59.1%) than in others (25.0%), but the mortality rate of all carcinoma cases receiving uni- or bilateral mastectomy (35.7%) was almost equal to that of the cases receiving partial mastectomy (34.8%).

Factors significantly ( $p<0.05$ ) associated with longer survival time of 78 dogs with epithelial MGTs were small-breed, small-sized tumor, histological diagnosis as benign and lower histological stage. In the multivariate analysis including these factors, statistical significance was detected in breed ( $p=0.048$ ) and histological stage ( $p=0.006$ ).

In 36 dogs with carcinomas, Kaplan-Meier survival rates at 1 and 2 years after surgery were 61.1 and 58.3%, respectively. The 2-year survival rates of small-breed (77.9%) or small-sized tumor (76.2%) groups were higher than those of other-breed (45.5%) or large-sized tumor (42.1%) groups though significant differences were not detected (breed;  $p=0.083$ , tumor size;  $p=0.072$ ). In all factors tested, histological stage showed a significant association with survival time ( $p=0.0189$ ). The 2-year survival rates of cases in stage 0, I, and II were 100, 69.2, and 38.9%, respectively (Fig. 2).

In this case series, small-breed dogs such as Maltese or Yorkshire terrier were predominant as in previous studies in Japan [4,13]. The incidence of malignancy in all cases (38.6%) was within the typical range reported in foreign

Table 1. Case distribution classified by histological evidence in small-breed dogs and others

Group	Benign mixed Tumor	Epithelial tumors						Sarcoma	Total
		Benign	Malignant	Histological stage <sup>a)</sup>			Total		
				0	I	II			
Small-breed	10 (0) <sup>b)</sup>	35 (0)	14 (3)	35 (0)	7 (1)	7 (2)	49 (3)	1 (1)	60 (4)
Others	8 (0)	9 (0)	23 (10)	12 (0)	9 (1)	11 (9)	32 (10)	1 (1)	41 (11)

a) Staged by tumor cell invasiveness as follows: stage 0; not invaded surrounding stroma, I: invaded stroma without vascular invasion, II: vascular invasion.

b) Numbers in parentheses indicate cases that died of mammary tumors.

Table 2. Case distribution classified by size of epithelial tumors in small-breed dogs and others

Group	All cases		Carcinoma cases	
	< 3 cm <sup>a)</sup>	≥ 3 cm	< 3 cm	≥ 3 cm
Small-breed	38 (0) <sup>b)</sup>	11 (3)	9 (0)	5 (3)
Others	16 (2)	16 (8)	9 (2)	14 (8)

a) Maximal diameter of tumors.

b) Numbers in parentheses indicate cases that died of mammary tumors.

Table 3. Case distribution classified by type of surgery for epithelial tumors in small-breed dogs and others

Group	All cases		Carcinoma cases	
	PM <sup>a)</sup>	UBM <sup>b)</sup>	PM	UBM
Small-breed	20 (2) <sup>c)</sup>	29 (1)	6 (2)	8 (1)
Others	24 (6)	8 (4)	17 (6)	6 (4)

a) Partial mastectomy. b) Uni- or bilateral mastectomy. c) Numbers in parentheses indicate cases that died of mammary tumors.

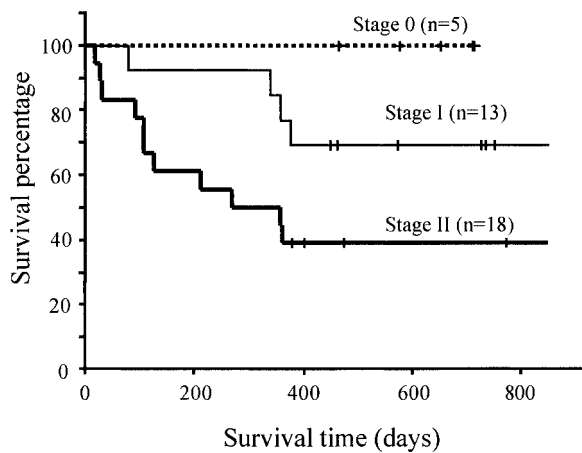


Fig. 2. Kaplan-Meier survival curves of 36 dogs with mammary carcinomas, stratified by histological stage of tumor cell invasion.

countries [8], but it was different between small-breed dogs (25.0%) and others (58.5%). Similar trend was confirmed in 299 canine MGTs recently diagnosed at the same institution: the rates of malignancy in 163 small-breed dogs and 133 others were 25.2 and 49.3%, respectively. Although possible inconsistency of histological criteria to assess malignancy among the cases limits the reliability of the epidemiological evaluation [3], the results of histological staging or survival analysis also indicated the lower rate of malignancy in small-breed dogs.

Gilbertson *et al.* [3] reported the utility of the histological stage of tumor invasion to predict recurrence of epithelial MGTs after surgery. Our results indicated its value to predict patient's survival even in the carcinoma cases as reported previously [13]. The comparatively better prognosis in small-breed dogs, even in the stage II cases, may be related to the small size of the tumor known as an important prognostic factor [6–9, 13] rather than the type of surgery which reportedly not influences the prognosis [7, 11]. In Japan, the higher survival rate (92.4%) of 159 dogs with malignant MGTs without distant metastasis at surgery, mainly consisting of small breeds, was reported [13]. In the series, stage 0 (non-infiltrative; 124 dogs) or small-sized tumors (< 3 cm; 119 dogs) were predominant. Another study in Japan showed that the 80.6% of 201 MGTs in small-breed dogs were small-sized tumors (< 3 cm) [5]. These results together with our findings indicated the higher rate of non-invasive or small-sized MGTs in small-breeds, possibly resulting in good prognosis of malignant MGTs in Japan, depending on the diagnostic criteria used. Therefore,

in the post-surgical managements for MGTs diagnosed as malignant, clinicopathological features such as tumor size or histological stage should be considered together.

In this study, 27.7% of all dogs were Malteses, which is obviously the higher percentage among the total dog population in Miyazaki prefecture, suggesting the higher risk of this breed as seen in previous reports [4, 13]. The later time of spaying in small breeds, suggested by the higher rate of intact female in this series, is known to increase the risk developing MGTs [2, 7, 12]. In addition, earlier detection of the palpable mass by the owner in small-breeds may contribute to the higher rate of small-sized MGTs [4, 13]. All these factors can influence the epidemiological feature of MGTs in Japan, which may limit the use of historical control from foreign countries when treatments are evaluated. Since the population of dogs was limited in this study, a particular tendency in representative breed such as Maltese or Yorkshire terriers is still unclear. A larger-scale study using uniformed histological criteria is needed to clarify the epidemiological feature of canine MGTs in Japan.

#### REFERENCES

1. Bostock, D. E., Moriarty, J. and Crocker, J. 1992. *Vet. Pathol.* **29**: 381–385.
2. Dorn, C. B., Taylor, D. O. N., Schneider, R., Hibbard, H. H. and Klauber, M. R. 1968. *J. Nat. Cancer Inst.* **40**: 307–318.
3. Gilbertson, S. R., Kurzman, I. D., Zachrau, R. E., Hurvitz, A. I. and Black, M. M. 1983. *Vet. Pathol.* **20**: 127–142.
4. Hashimoto, S., Yamamura, H., Sato, T., Kanayama, K. and Sakai, T. 2002. *J. Vet. Epidemiol.* **6**: 85–90.
5. Hellmen, E., Bergstrom, R., Hornberg, L., Spangberg I. B., Hansson, K. and Lindgren, A. 1993. *Vet. Pathol.* **30**: 20–27.
6. Philibert, J. C., Synder, P. W., Glickman, N., Glickman, L. T., Knapp, D. W. and Waters, D. J. 2003. *J. Vet. Intern. Med.* **17**: 102–106.
7. Macwen, E.G. and Withrow, S. J. 1996. *Small Animal Clinical Oncology*, 2nd ed., W. B. Saunders, Philadelphia.
8. Misdorp, W., Else, R. W. and Lipscomb, T. P. 1999. *Histological Classification of Mammary Tumors of the Dog and Cat*, 2nd series, Vol. VII, American Registry of Pathology, Washington, D. C.
9. Misdorp, W. and Hart, A. A. M. 1976. *J. Nat. Cancer Inst.* **56**: 779–786.
10. Rostami, M., Tateyama, S., Uchida, K., Naitoh, H., Yamaguchi, R. and Otsuka, H. 1994. *J. Vet. Med. Sci.* **56**: 403–405.
11. Sorenmo, K.U., Shofer, F. S. and Goldschmidt, M. H. 2000. *J. Vet. Intern. Med.* **14**: 266–270.
12. Vos, J. H., Ingh, T. S. G. A. M. van den, Misdorp, W., Molenbeek, R. F., Mil, F. N. van, Rutteman, G. R., Ivanyi, D. and Ramaekers, F.C.S. 1993. *Vet. Quart.* **14**: 96–102.
13. Yamagami, T., Kobayashi, T., Takahashi, K. and Sugiyama, M. 1996. *J. Vet. Med. Sci.* **58**: 1079–1083.