Prognosis for Canine Malignant Mammary Tumors Based on TNM and Histologic Classification

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ABSTRACT. The 2-year prognosis of malignant mammary tumors seen in 175 bitches in the Tokyo metropolitan area was assessed based on their TNM clinical staging and histological classification. The larger the tumor size became (T category), the poorer was the clinical prognosis. The 2-year survival rates of the animals with regional lymph node metastasis of tumor cells (N1, N2 category) and/or distant metastasis (M1 category) were markedly lower than those of the animals without such involvement. As the grade of TNM staging increased, the prognosis was poorer, however, there were no significant differences in survival rates among subtypes of adenocarcinomas (tubular, papillary and papillary cystic) determined by WHO histological classification. It was also noticed that animals having carcinomas without tubular formation or myoepithelial cell proliferation had a lower survival rate than animals having carcinomas with those characteristics; and invasive carcinomas into adjacent skin or lymphatic/vascular vessels implied a poorer prognosis than non-invasive ones. The results suggest that a combined practice of TNM system and our evaluation on the above-mentioned 4 histologic features could be useful for prognostic determination of canine mammary cancers. — KEY WORDS: canine, mammary tumor, prognosis, TNM classification.

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Next to skin tumors, mammary tumors are the most commonly occurring neoplasms in dogs [22], and their biological behavior has been well documented [1, 4, 6, 8, 11, 14, 15, 16, 23]. However, various factors such as complicated histologic types, site distribution, onset time, biological behavior, etc., make it difficult to make a prognosis. Although many efforts have been made to find a correlation between histologic type and clinical prognosis [6, 9, 10, 14, 17, 26], no reliable criteria have yet been established. Some studies have suggested that tumor size, or certain types of morphological features may be have prognostic value [4, 5, 14, 17]. Weijer and others [28] showed that histological grading of feline mammary carcinomas had a prognostic significance, however, in dogs clinical staging seems to be of greater significance than histological grading [2]. In general, attention has been paid to histologic type, rather than surveys of clinical information. There are considerable variations in biological behavior even among tumors histologically diagnosed malignant, and in mammary tumors in dogs, myoepithelial cell proliferations are more or less present with neoplastic secretory cells and sometimes predominate. The role these cells play in mammary tumors remains unclear.

In a series of canine mammary tumors seen in dogs in the Tokyo metropolitan area, the present study was done focussing attention on the following aspects: 1) to determine whether there is a correlation between clinical staging based upon the TNM system and biological behavior; 2) to make a comparison with data reported in foreign countries; and 3) to seek some prognostic aids from a combination of clinical staging and histologic observation.

MATERIALS AND METHODS

Three hundred sixty-two cases of canine mammary tumors were randomly chosen from the biopsy files of the Department of Veterinary Pathology at the Nippon Veterinary and Animal Science University. These tumors were excised surgically from bitches in several animal hospitals located in the Tokyo metropolitan area from 1986 through 1992, and then sent to the Department of Veterinary Pathology for histological diagnosis. After being fixed immediately in 10% neutral buffered formalin solution, all surgical specimens were embedded in paraffin wax and cut at 3 μm. The paraffin sections were stained with hematoxylin and eosin (HE) and, if necessary, other stains including immunostains were employed. The tumors were diagnosed according to the classification of canine mammary tumors proposed by Hampe and Misdorp [12], and the clinical data of the animals were followed up retrospectively for at least 2 years after surgical excision of the mammary neoplasm. The cases that died from "other" causes not related to mammary tumors, or that underwent anticancer chemotherapy were excluded from this study, because, especially in the latter, treatment might have modified the original biological behavior of the tumors. Finally, we selected 175 mammary tumors which were histologically determined to be malignant, and whose follow-up data were available. These 175 bitches consisted of various breeds: Maltese (38), Yorkshire terrier (27), Poodle (17), Shih tzu (11), Pomeranian (8), Shetland sheepdog (7), Shiba (6), Dachshund (5), Beagle (4), Mongrel (34) and others (18). The age distribution of the bitches at the time of tumor excision is shown in Fig. 1. The tumors were categorized according to the TNM system (T, maximum diameter of the

primary tumor, T1 – less than 3 cm. , T2 – 3–5 cm. , T3 – more than 5 cm. , T4 – any size, inflammatory carcinoma; N, involvement of the regional lymph nodes (RLN), N0 - not evident, N1 – ipsilateral, N2 – bilateral; and M, distant metastasis, M0 - absent, M1 - present) proposed by the World Health Organization [25]. When one animal had multiple mammary tumors, the tumor in the bearer was represented by the most malignant, which was microscopically determined, and was used for stage grouping of TNM classification. The original TNM classification requires histological information of RLN for stage grouping of canine mammary tumors. In practice, however, radical excision of RLN was seldom performed in T0 (no evidence of tumor) or T1 (tumor < 3cm) cases unless the node involvement was clinically evident. Thus, RLN devoid of any clinical abnormality was evaluated as N0 in this study.

The Kaplan-Meier method was employed to describe 2-year cumulative survival curves, and the correlation between each category and prognosis was assessed by the Cox-Mantel method. The procedure was performed using freeware for Macintosh named Hyper Kaplan version 3.6.

RESULTS

Relationship between TNM classification and prognosis: A high incidence of malignant mammary tumors was noted in the dogs aged 6 to 12 years (Fig. 1), average age 9.1 years (range 1–18 years). In general, the larger the tumors were (T category), the poorer was the clinical prognosis (Fig. 2). The animals with tumors invading adjacent skin (T4) showed the lowest survival rate (53.3%). The survival rate (35.7%) of the animals with tumors involving regional lymph node (N2) was markedly lower than 94.4% of the animals without such involvement (N0) (Fig. 3). Furthermore, distant metastasis gave rise to an accelerated demise of the affected animals (M0 92.4%, M1 13.6%) (Fig. 4).

The relationship between stage grouping of TNM classification and survival rate is shown in Fig. 5. The stage 2 (T0, N1+, M0, T1, N1+, M0, and T2, N0+ or N1+, M0) group was unavailable for statistical analysis because the total number (3) of cases was extremely small compared to those of the other 3 groups. As the grade of staging increased, the prognosis was poorer. The survival rates in the stage 4 (anyT, anyN, M1), 3 (anyT, anyN, M0) and 1 (T1, N0, M0) group were respectively, 13.6%, 75.8% and 97.9% one year after mastectomy, and 13.6%, 66.4% and 97.9% 2 years after mastectomy.

Relationship between histologic type and prognosis: There was no significant difference in the prognosis among histopathological subtypes (tubular, papillary and papillary cystic) of adenocarcinomas (Fig. 6). On the other hand, the 2-year survival rates (60.8%) of the animals with non-tubular tumors such as solid carcinomas, anaplastic carcinomas and squamous cell carcinomas were significantly lower ($p<0.01$) than 93.8% of adenocarcinomas and 83.3% of mixed malignant tumors (Fig. 7).

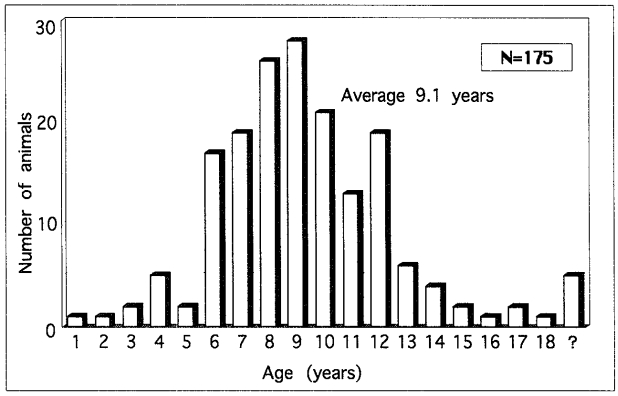

Fig. 1. Age distribution in 175 bitches at time of tumor excision.

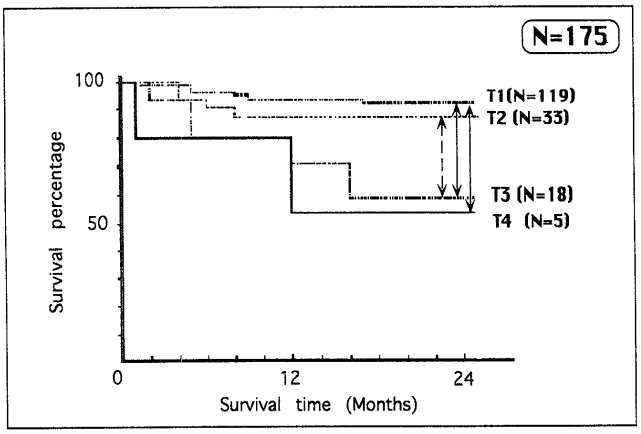

Fig. 2. Survival percentage according to tumor size. T1-Tumor < 3 cm. maximum diameter, T2-Tumor 3–5 cm. maximum diameter, T3-Tumor >5 cm. maximum diameter, T4-Tumor any size, inflammatory carcinoma.⬅···➡: $p<0.05$, ⬅—➡: $p<0.01$

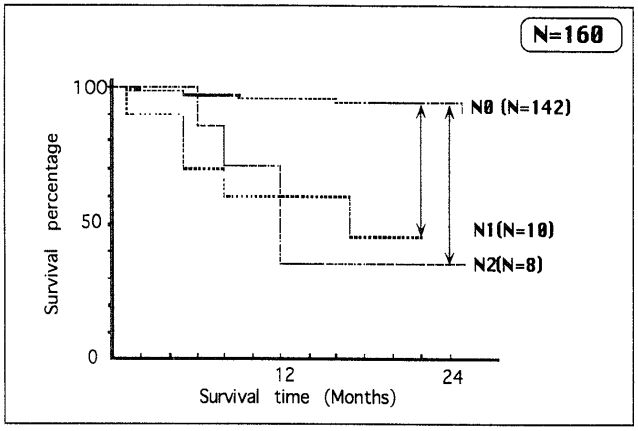

Fig. 3. Survival percentage according to regional lymph node (RLN) status. N0 - no evidence of RLN involvement, N1 - ipsilateral RLN involved, N2 - bilateral RLN involved. ⬅—➡: $p<0.01$

Other histologic features possibly associated with prognosis: The following 4 histologic features were noticed relating to prognosis and assessed for statistical analysis:

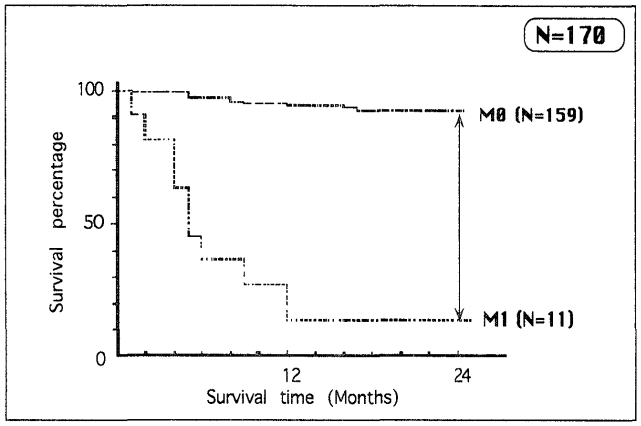

Fig. 4. Survival percentage according to metastasis. M0 - no evidence of distant metastasis, M1 - distant metastasis including distant nodes. ⟵⟶: $p<0.01$

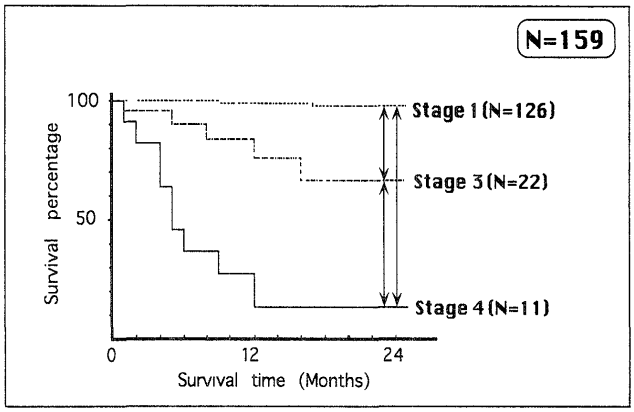

Fig. 5. Survival percentage according to TNM classification. Stage 1 - T1, N0, M0, Stage 3 - any T, any N, M0, Stage 4 - any T, any N, M1. ⟵⟶: $p<0.01$

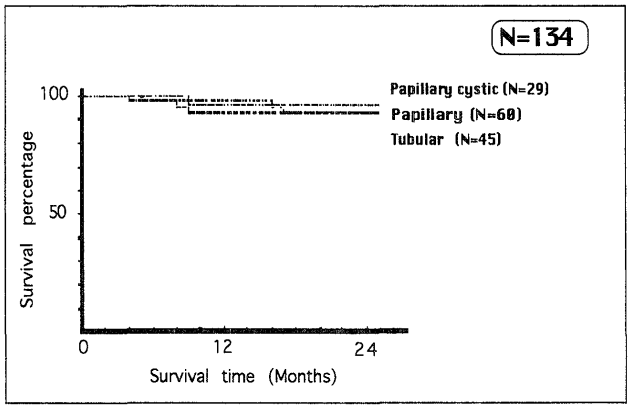

Fig. 6. Survival percentage according to histological subtypes of adenocarcinoma.

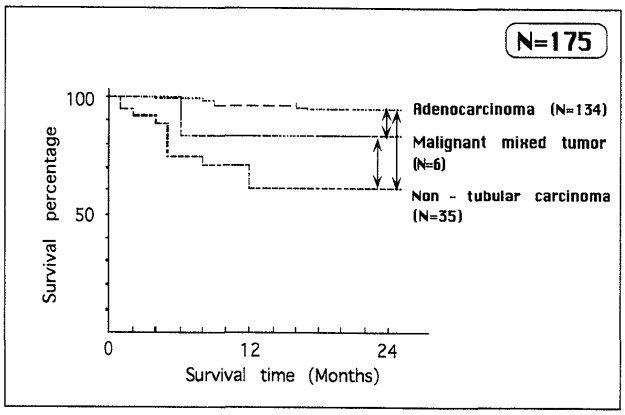

Fig. 7. Survival percentage according to modified histologic classification. Non-tubular carcinoma: solid carcinomas (N=29), anaplastic carcinomas (N=2) and squamous cell carcinomas (N=4). ⟵⟶: $p<0.01$

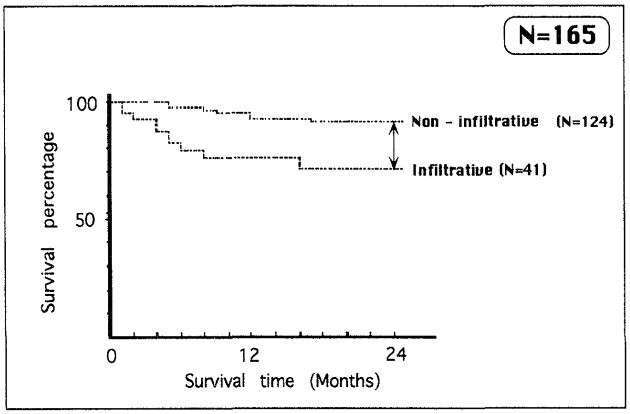

Fig. 8. Survival percentage according to infiltration of tumors. ⟵⟶: $p<0.01$

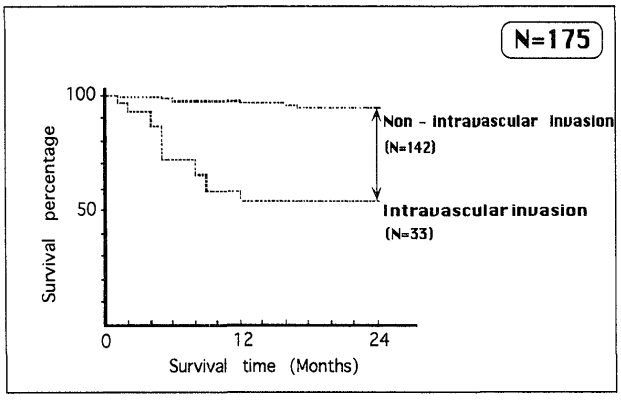

Fig. 9. Survival percentage according to vascular/lymphatic permeation of tumors. ⟵⟶: $p<0.01$

(a) tubular formation; (b) myoepithelial cell proliferation; (c) infiltration of tumor cells into adjacent tissue; and (d) vascular or lymphatic permeation of tumor cells. The bitches with tumors which were of a non-tubular (Fig. 7), infiltrative (Fig. 8) and/or permeative (Fig. 9) type had a significantly lower ($p<0.01$) 2-year survival rate than those with tumors showing no such features. Whereas, the bitches with tumors including proliferative myoepithelial cells had a significantly higher ($p<0.01$) survival rate than those with tumors consisting of secretory cells alone (Fig. 10).

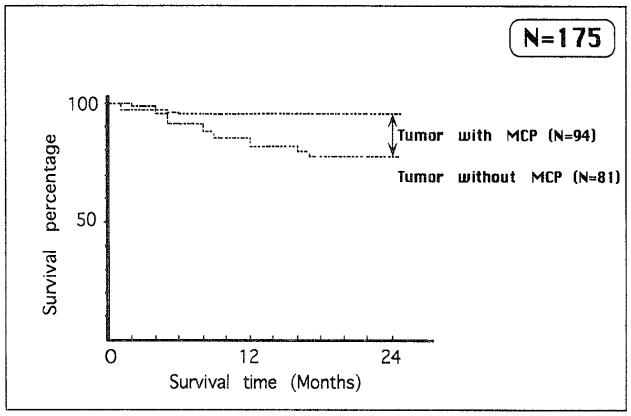

Fig. 10. Survival percentage according to myoepithelial cell proliferation (MCP). ⬅—➡: $p<0.01$

DISCUSSION

Canine mammary tumors generally increase in incidence with aging. The incidence increases rapidly at the onset of "cancer age (6–7 years of age)", whereas the occurrence is rare in dog less than 2 years old [22]. In this series presented here, the same trend was noted and the average age, 9.1 years old, at the time of tumor excision, is comparable to those reported elsewhere [5, 6, 14, 20].

The breed popularity in the geographical areas where the tumors were obtained is probably responsible for the breed distribution of the tumors. In the Tokyo metropolitan area, where the tumors were sampled in this study, miniature dogs, kept indoors, are the predominant household pets, and therefore were the most commonly affected breed. The owners of these companion animals often had a chance to touch them, so they could relatively easily find out any surface abnormalities at an early stage. According to tumor size, the T1 category (tumor < 3 cm, maximum diameter) of TNM classification [25] was predominant (119 cases). This would cause an overall high survival percentage in this study despite morphological evidence of malignancy when compared with previous reports [3, 27].

This study indicates that the animals with carcinomas accompanied by myoepithelial cell proliferation (complex type) had a longer survival time than those with adenocarcinomas composed of secretory cells alone (simple type). It is well known that canine mammary carcinomas show different growth patterns and different biological behavior depending on whether the tumors are simple or complex [17, 18]. The tumors of the complex type appear to be biologically less malignant than those of the simple type [12]. The simple type of carcinoma generally grows in a highly infiltrative manner, invades lymph vessels, and spreads to regional lymph nodes, distant lymph nodes and the lung. Whereas, the complex type of carcinoma often grows in a more expansive "pushing" manner, invades lymph vessels and less frequently metastasizes to the lymph nodes and lung. Therefore, active myoepithelial cells might play a role in suppressing proliferation or invasion of the neoplastic secretory cells, although the mechanism remains unclear.

It has been disputed as to whether tumor cell invasion in the lymphatic vessel or lymph nodes is deeply associated with poor prognosis. In general, such findings are highly malignant and imply a possible distant metastasis in the future, leading to a poor prognosis [14, 19, 22]. Our present data also indicate that invasive carcinomas accompany a significant decrease in survival rate when compared with carcinomas having a non-invasive nature, although, Misdorp and Hart [17] found no relationship between these histologic features and survival rate. Approximately a half or more of the cases in our series that showed intravascular invasion of the tumor cells survived for 2 years after mastectomy without any clinical abnormalities. This suggests that the findings of vascular or lymphatic permeation of the tumor cells on the sections are not necessarily a definitive indicator for poor prognosis.

Recently some studies suggested that progesterone receptor, estrogen receptor, epidermal growth factor receptor [15, 24], nuclear DNA content [21] and oncogene expression [7] could serve as new prognostic parameters for canine mammary tumors, but there are some technical difficulties in carrying out these examinations routinely. As an alternative, we have demonstrated that some histological features such as tubular formation, infiltration and vascular permeation of tumor cells, and myoepithelial cell proliferation could be of prognostic value for malignant mammary tumors in dogs. Mutivariate analysis indicates that these parameters are not independent of each other (data not shown), therefore, these histological features might be phenomena related to each other. In order to verify this hypothesis, another study concerning cellular interaction between epithelial cells and mesenchymal cells, and/or between secretory cells and myoepithelial cells needs to be carried out.

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