

# Prognostic factors associated with survival two years after surgery in dogs with malignant mammary tumors: 79 cases (1998–2002)

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**Objective**—To identify prognostic factors for female dogs that have undergone surgical removal of malignant mammary tumors.

**Design**—Retrospective case series.

**Animals**—79 female dogs with malignant mammary tumors.

**Procedure**—Information obtained from the medical records included breed, age, sex, tumor size (maximum diameter), number and location of affected mammary glands, time between tumor identification and surgical removal, radiographic evidence of distant metastasis, surgical procedure, ovariectomy (OHE) status, histologic classification of the tumor, and survival time.

**Results**—Results of univariate analyses indicated that clinical stage, tumor size, OHE status, metastasis to adjacent lymph nodes or distant sites, and histologic classification of the tumor were significantly associated with survival 2 years after surgery. Tumors  $\geq 5$  cm in diameter and tumors that had been identified  $> 6$  months before surgery were more likely to metastasize to adjacent lymph nodes. Ovariectomy was more beneficial in dogs with complex carcinomas than in dogs with simple carcinomas. In multivariate analyses, clinical stage, tumor size, and OHE status were significantly associated with survival 2 years after surgery.

**Conclusions and Clinical Relevance**—Results suggest that tumor stage, tumor size, and OHE status were significant prognostic factors associated with survival 2 years after surgery in dogs with malignant mammary tumors. Further, either dogs with tumors  $\geq 5$  cm in diameter or dogs with tumors present for  $> 6$  months prior to surgery had a higher risk of having lymph node metastases. (*J Am Vet Med Assoc* 2005;227:1625–1629)

Mammary carcinoma is the most common malignant neoplasm in female dogs,<sup>1</sup> with surgical removal being the most common treatment for dogs with most types of mammary tumors.<sup>2,3</sup> Several studies have identified factors associated with outcome of dogs undergoing surgery for removal of mammary tumors. Age, for

example, has been shown to be associated with outcome for such dogs, with diagnosis of mammary tumors at a later age reported to be a negative prognostic factor,<sup>4,5</sup> although 1 study<sup>6</sup> did not find any significant association between age and outcome. Tumor size has been found to be an independent prognostic factor in several studies,<sup>7-10</sup> and 2-year survival rates for dogs with regional lymph node or distant metastasis were markedly lower than rates for dogs without such involvement.<sup>10</sup> Tumor type has been reported to be significantly associated with outcome in a number of studies,<sup>5,7-11</sup> with dogs that have high histologic grade mammary tumors more likely to have a poor prognosis.

For other potential prognostic factors, however, conflicting results have been reported. For instance, several studies<sup>4,6,12,13</sup> have shown that performing an ovariectomy (OHE) at the time of or after mammary tumor excision does not significantly affect survival time, but 1 study<sup>14</sup> found that performing OHE at the time of or  $< 2$  years before tumor removal improved survival rate. In addition, although it might be considered likely that the time between identification of a tumor and its surgical removal would be associated with prognosis, only a limited study<sup>8</sup> has been done to determine the effect that time between tumor identification and removal might have on survival time in dogs with malignant mammary tumors.

For these reasons, more information is needed on possible prognostic factors following surgical removal of malignant mammary tumors in dogs. The purpose of the study reported here was to identify prognostic factors in female dogs that have undergone surgical removal of malignant mammary tumors.

## Criteria for Selection of Cases

Medical records of all dogs examined at the Veterinary Medical Teaching Hospital of the National Chung-Hsing University between 1998 and 2002 that were found to have mammary tumors were reviewed. Cases were eligible for inclusion in the study if the diagnosis of a malignant mammary tumor had been confirmed by means of histologic examination and adequate follow-up information was available.

## Procedures

Information obtained from the medical records included breed, age, sex, tumor size, number and location of affected glands, time between tumor identification and surgical removal (ie, **observed time [OT]**), radiographic evidence of distant metastasis, surgical

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procedure, OHE status, histologic classification of the tumor, and survival time. Surgical procedure was classified as lumpectomy (removal of the tumor only), simple mastectomy (removal of the affected gland only), modified radical mastectomy (removal of the affected gland and glands that shared lymphatic drainage along with removal of associated lymph nodes), or radical mastectomy (removal of the entire mammary chain and associated lymph nodes either unilaterally or bilaterally).<sup>15</sup> The extent of the resection was determined by the size, location, and number of tumors and the clinical status of regional lymph nodes.

Clinical stage was assigned according to the TNM system.<sup>16</sup> Tumor size was identified as maximum diameter. Whether lymph node metastasis had occurred was determined by means of histologic examination. Whether distant metastasis had occurred was determined by means of radiography or necropsy. Excised mammary tumors were fixed in neutral-buffered 10% formalin and processed by means of standard histologic techniques. Sections stained with H&E were examined, and tumor type was determined by use of the World Health Organization–Air Force Institute of Pathology classification system for canine mammary tumors.<sup>25</sup>

For all dogs, it was recommended that follow-up examinations, including thoracic radiography, be performed every 1 to 2 months for the first 6 months after surgery. After this time, owners were interviewed by telephone every 6 to 12 months and follow-up examinations were scheduled as necessary. Owners of some dogs that died or were euthanatized were asked for permission to perform a postmortem examination. In dogs that died of causes unrelated to the malignant mammary tumors, death was not considered to be a result of the malignant mammary tumors.

**Statistical analysis**—Overall survival time was calculated from the date of surgical removal of the tumor to the date of death or the last date of follow-up. In dogs that died of causes unrelated to the mammary tumors, the date of death was defined as the censored date for calculating survival time. The Kaplan-Meier method was used to compute overall survival time and to construct category-specific survival curves.<sup>17</sup> The log-rank test was used to identify factors associated with survival 2 years after surgery.<sup>18</sup> The Pearson  $\chi^2$  test was used to test for associations between categorical factors. The Cox proportional hazards model was used for univariate and multivariate analyses of factors potentially associated with survival 2 years after surgery.<sup>19</sup> Variables of biological importance or that were found to be significant in univariate analyses were selectively included in the multivariate model. For all analyses, values of  $P \leq 0.05$  were considered significant. All analyses were performed with commercial software.<sup>a</sup>

## Results

**Signalment**—Records of 79 dogs with malignant mammary tumors met the criteria for inclusion in the study. There were 30 mixed-breed dogs, 12 Maltese, 5 Pomeranians, 5 German Shepherd Dogs, 5 Rottweilers, 4 Toy Poodles, 4 Akitas, 2 Cocker Spaniels, 2 Old English Sheepdogs, 1 Shih-Tzu, 1 Shetland Sheepdog,

1 Dachshund, 1 Spitz, 1 Chihuahua, 1 Dalmatian, 1 Yorkshire Terrier, 1 Beagle, 1 Pekingese, and 1 Lhasa Apso.

Mean age of the dogs at the time tumors were first identified by the owners was 8.4 years (range, 2 to 14 years; **Figure 1**), and mean age at the time of surgery was 9.9 years (range, 3 to 16 years). Mean  $\pm$  SD tumor size (ie, maximum tumor diameter) was  $7.2 \pm 4.9$  cm (range, 0.5 to 21 cm). In 28 (35%) dogs, OHE was done before, after, or at the time of mammary tumor removal. In 15 of these 28 dogs, OHE was performed because of pyometra.

Mean  $\pm$  SD OT (ie, time between tumor identification and surgical removal) was  $18.4 \pm 17.0$  months (range, 1 to 96 months). Mean survival time was  $14.2 \pm 8.8$  months (range, 1 to 24 months).

**Factors associated with prognosis**—In univariate analyses, histologic classification of the tumor, clinical stage, tumor size, OHE status, metastasis to adjacent lymph nodes, and distant metastasis were significantly associated with survival 2 years after surgery (**Table 1**). Median survival time after surgery was 6 months for dogs with clinical stage IV or V malignant mammary tumors, whereas most dogs with clinical stage I, II, or III tumors were still alive 6 months after surgery (**Figure 2**). Survival curves for dogs grouped on the basis of histologic type differed only for dogs with stage I, II, or III tumors and not for dogs with stage IV or V tumors (**Figure 3**).

Dogs that had undergone OHE were more likely to have survived 2 years after surgery than were dogs that had not (**Figure 4**). Analysis of histologic type for dogs that did or did not undergo OHE indicated that OHE

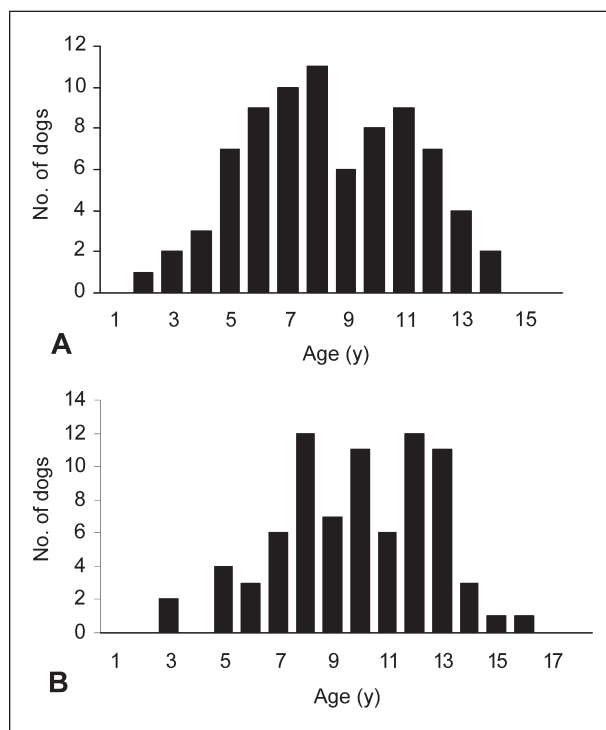


Figure 1—Age at the time tumors were first identified (A) and at the time of surgical removal (B) in 79 dogs with malignant mammary tumors.

Table 1—Results of univariate analysis of variables possibly associated with survival 2 years after surgery in dogs that underwent surgical removal of malignant mammary tumors.

Variable	No. of dogs (%)	RH	95% CI
<b>Histologic classification</b>			
Simple carcinoma	18 (23)	Referent	NA
Complex carcinoma	50 (63)	1.82	0.68–4.83
Sarcoma	11 (14)	4.12	1.27–13.31
<b>Clinical stage</b>			
Stage I, II, or III	34 (43)	Referent	NA
Stage IV or V	45 (57)	10.11	3.51–29.11
<b>Tumor size*</b>			
< 5 cm	30 (38)	Referent	NA
≥ 5 cm	49 (62)	6.89	2.39–19.81
<b>OHE</b>			
No	51 (65)	Referent	NA
Yes	28 (35)	0.38	0.17–0.81
<b>Breed</b>			
Mixed (5–45 kg [11–100 lb])	29 (37)	Referent	NA
Toy or small (≤ 10 kg [22 lb])	32 (40)	0.87	0.40–1.89
Large (> 10 kg [22 lb])	18 (23)	1.16	0.48–2.76
<b>Side of affected gland</b>			
Left	25 (32)	Referent	NA
Right	19 (24)	0.93	0.38–2.30
Both	35 (44)	0.85	0.36–1.97
<b>Location of affected gland</b>			
Cranial (glands 1, 2, and 3)	12 (15)	Referent	NA
Caudal (glands 4 and 5)	37 (47)	2.49	0.69–9.00
Both	30 (38)	3.04	0.88–10.51
<b>Surgical procedure</b>			
Radical mastectomy	10 (13)	Referent	NA
Modified radical mastectomy	33 (42)	2.21	1.03–25.18
Simple mastectomy	24 (30)	0.59	0.05–3.66
Lumpectomy	7 (9)	0.41	0.17–2.10
Biopsy	5 (6)	5.09	0.74–6.56
<b>Lymph node metastasis</b>			
No	44 (56)	Referent	NA
Yes	35 (44)	5.16	2.44–10.88
<b>Distant metastasis</b>			
No	49 (62)	Referent	NA
Yes	30 (38)	3.54	1.74–7.21
<b>Observed time†</b>			
≤ 6 months	20 (25)	Referent	NA
> 6 but ≤ 12 months	25 (32)	2.45	0.94–6.37
> 12 months	34 (43)	1.17	0.44–3.11

Data were obtained from 79 dogs, of which 34 had died by the time of the study. All relative hazards were adjusted for age at the time of surgery.  
 \*Maximum tumor diameter. †Time between tumor identification by the owner or attending veterinarian and surgical removal.  
 RH = Relative hazard. CI = Confidence interval. OHE = Ovariohysterectomy.

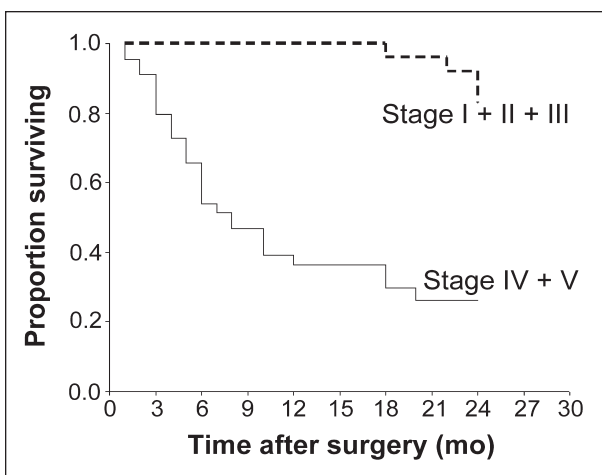


Figure 2—Kaplan-Meier survival curves following surgical removal of malignant mammary tumors for 79 dogs grouped on the basis of clinical stage.

was beneficial in dogs with complex carcinoma but provided less of a benefit in dogs with simple carcinoma (Figure 5). Overall, 28% of dogs with simple carcinomas, 42% of dogs with complex carcinomas, and 18% of dogs with sarcomas had undergone OHE. Ovariohysterectomy was no longer associated with survival 2 years after surgery after stratification by clinical stage.

Thirty of the 35 (86%) dogs with evidence of lymph node metastasis had tumors ≥ 5 cm in maximum diameter, compared with 19 of the 44 (43%) dogs without evidence of lymph node metastasis. Tumor size (< 5 vs ≥ 5 cm in maximum diameter) was significantly ( $P < 0.001$ ) associated with detection of lymph node metastasis (yes vs no), with dogs with lymph node metastasis more likely to have tumors ≥ 5 cm in diameter (odds ratio, 7.9; 95% confidence interval, 2.58 to 24.17) than dogs without lymph node metastasis.

Similarly, 30 of the 35 (86%) dogs with evidence of lymph node metastasis had OTs > 6 months, compared with 29 of the 44 (66%) dogs without evidence of lymph node metastasis. Observed time (> 6 vs ≤ 6 months) was significantly ( $P = 0.044$ ) associated with detection of lymph node metastasis, with dogs with lymph node metastasis more likely to have OTs > 6

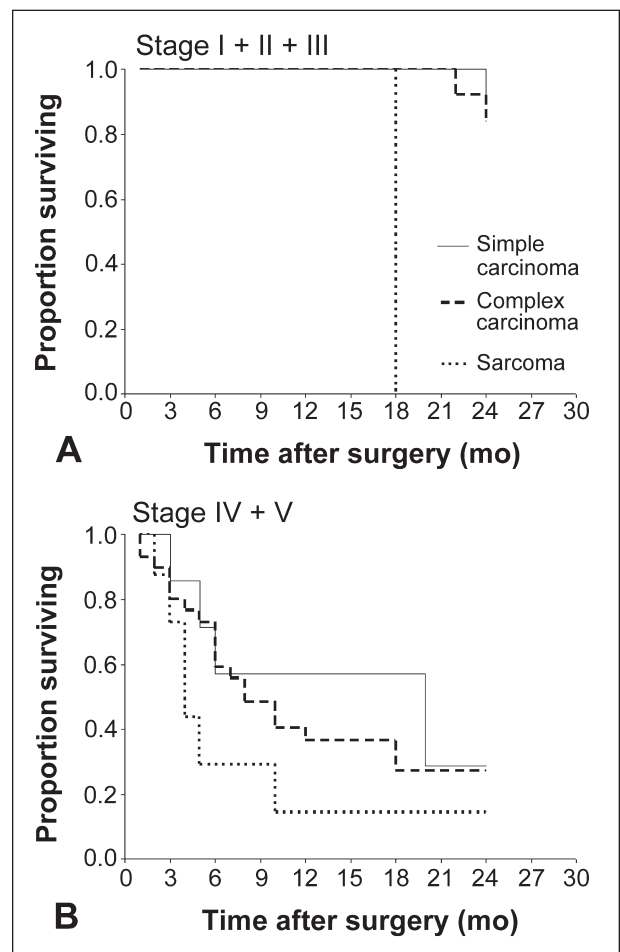


Figure 3—Kaplan-Meier survival curves following surgical removal of malignant mammary tumors for 79 dogs grouped on the basis of histologic tumor type. A—Dogs with stage I, II, or III tumors. B—Dogs with stage IV or V tumors.

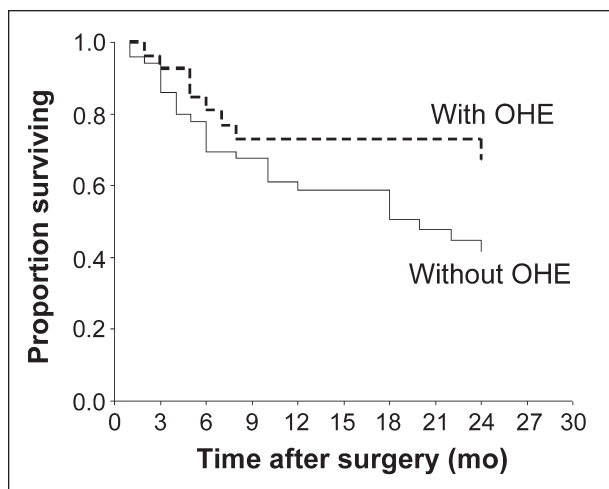


Figure 4—Kaplan-Meier survival curves following surgical removal of malignant mammary tumors for 79 dogs grouped on the basis of whether they did or did not have a history of ovari-hysterectomy (OHE).

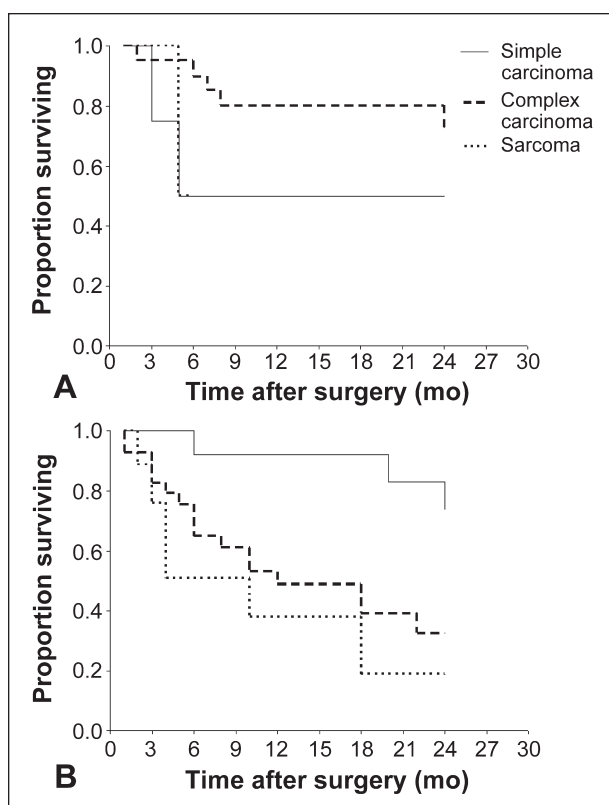


Figure 5—Kaplan-Meier survival curves following surgical removal of malignant mammary tumors for 79 dogs grouped on the basis of histologic tumor type. A—Dogs that had undergone OHE. B—Dogs that had not undergone OHE.

months (odds ratio, 3.10; 95% confidence interval, 1.00 to 9.64) than dogs without lymph node metastasis.

Variables found in univariate analyses to be significantly associated with survival 2 years after surgery were included in multivariate analyses. The most predictive multivariate model included age at the time of surgery, clinical stage, tumor size, OT, and OHE status (Table 2). After adjustment for age at the time of

Table 2—Results of multivariate analysis of factors associated with survival 2 years after surgery in dogs that underwent surgical removal of malignant mammary tumors.

Variable	Adjusted RH* (95% CI)	P value
Age at the time of surgery	1.12 (0.98–1.28)	0.087
Clinical stage (IV or V vs I, II, or III)	7.38 (2.26–24.09)	0.001
Tumor size ( $\geq 5$ vs $< 5$ cm)	3.68 (1.17–11.56)	0.026
OHE (yes vs no)	0.41 (0.17–0.98)	0.045
Observed time ( $> 6$ vs $\leq 6$ months)	0.45 (0.17–1.18)	0.105

\*Age-adjusted RH.  
See Table 1 for remainder of key.

surgery and OT, clinical stage, tumor size, and OHE status were still found to be significant prognostic factors for survival 2 years after surgery.

## Discussion

In the present study, we used a modification of the World Health Organization's staging system<sup>16</sup> to classify dogs with malignant mammary tumors so that the traditional 5 stages were grouped to provide 2 categories: dogs with stage I, II, or III tumors and dogs with stage IV or V tumors. With this modification, clinical stage was found to be a significant prognostic factor for survival 2 years after surgery, which was similar to results of a previous study.<sup>10</sup>

Mean age at the time of surgery for dogs in the present study was 9.9 years (range, 3 to 16 years), which was similar to ages reported in previous studies.<sup>5,12,13</sup> Mammary tumors were more likely to occur in middle-aged and old dogs, and in a previous study,<sup>5</sup> age was considered to be an important prognostic factor. In contrast, age was not found to be a significant prognostic factor in the present study. In contrast with age at the time of surgery, information on age at the time of tumor development has been rarely reported. In the present study, mean age at the time tumors were first noticed was 8.4 years old (range, 2 to 14 years).

Surgical technique was not found to be a significant prognostic factor in the present study, although relative hazard of death within 2 years after surgery was slightly higher for dogs that underwent modified radical mastectomy, compared with dogs that underwent radical mastectomy. In previous studies,<sup>4,8-10</sup> surgical technique also did not seem to be a significant prognostic factor for survival time as long as the entire tumor was removed.

Some researchers have suggested that the time tumors have been present prior to treatment is not important to prognosis, and OT was not found to be a significant prognostic factor in the present study. However, longer OT may promote enlargement of the tumor and increase the risk of lymph node or distant metastasis. In many instances, mammary tumors are not thought to be in a late stage of development when first detected by owners or clinicians. The complicated biologic characteristics of these tumors, however, make this difficult to predict clinically.<sup>5</sup> In the present study, lymph node metastasis was significantly associated with OT and dogs with lymph node metastasis were more likely to have OTs  $> 6$  months. Therefore, we suggest that an OT  $> 6$  months might be the critical time for malignant mammary tumors to metastasize.

size. None of the dogs with tumors < 3 cm in diameter in the present study had evidence of lymph node metastasis.

In dogs, OHE early in life significantly reduces the risk that mammary tumors will develop,<sup>4</sup> and in the present study, OHE was found to be a protective factor for dogs with malignant mammary tumors. In other studies,<sup>12,13</sup> OHE before or at the time of mastectomy was not a prognostic factor in dogs with established mammary gland neoplasms. In contrast, a recent report<sup>14</sup> suggested that OHE may be an effective adjunct to tumor removal in dogs with mammary gland carcinoma and that the timing of OHE plays a critical role in survival time. In the present study, OHE appeared to be more beneficial in dogs with complex carcinomas than in those with simple carcinomas.

In conclusion, tumor stage, tumor size, and OHE status were significant prognostic factors associated with survival 2 years after surgery in dogs with malignant mammary tumors. Further, dogs with tumors  $\geq 5$  cm in diameter and dogs in which tumors were present for > 6 months prior to surgery had a higher risk of having lymph node metastases. Dogs in which OHE had been performed had a better prognosis than dogs in which OHE had not been performed, especially if the dogs had complex carcinomas.

a. SPSS, version 10.0.7, SPSS Taiwan Corp, Taipei, Taiwan.

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