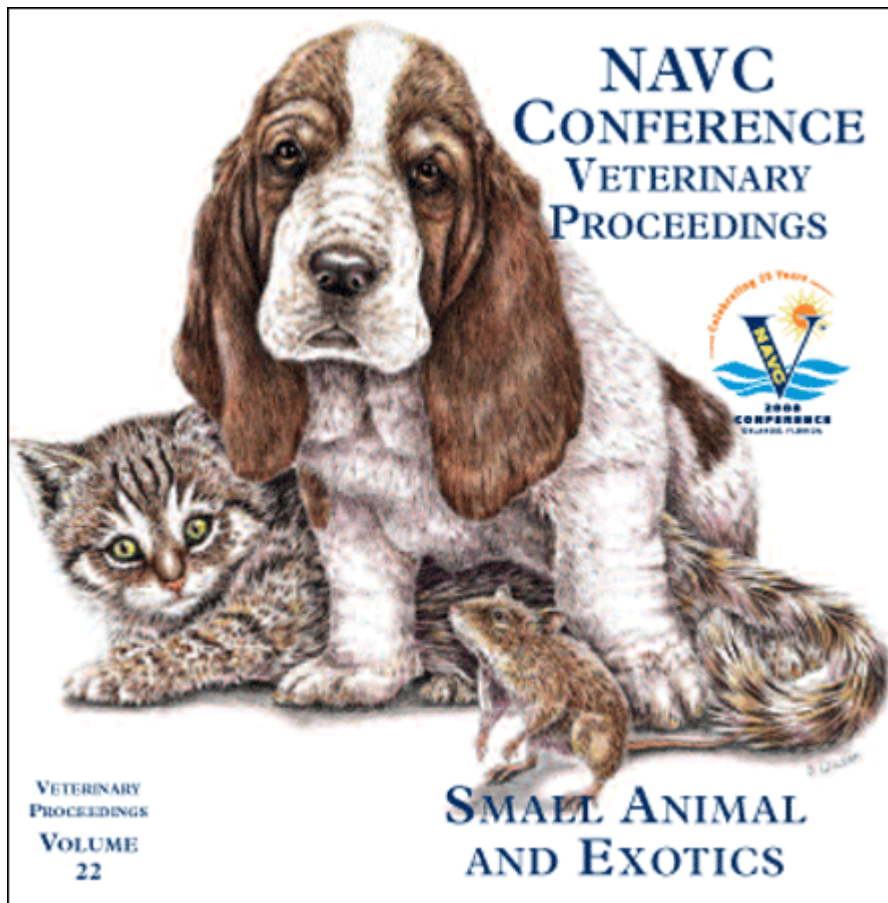


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MAMMARY GLAND TUMORS: YOUR QUESTIONS ANSWERED

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Despite the fact that mammary tumors are commonly encountered in veterinary practice, little progress has been made in the clinical management of mammary carcinoma in recent years. Of all neoplasms in female dogs, breast tumors represent 25% to 50%, and are the second most frequent class of neoplasm seen in dogs after skin tumors. In the cat, mammary glands are the third most common site of cancer after hematopoietic and skin tumors. Half of all dogs presented with mammary masses in veterinary practice will have benign disease that is surgically cured with ease. Of the 50% of dogs that present with mammary malignancy, a further one half are cured by adequate surgery. Thus 75% of dogs with mammary masses are cured with relatively straightforward management approaches. Veterinary oncologists and general practitioners face a twofold challenge with regard to mammary tumors. First, criteria must be established and accepted that identifies the 25% of dogs at risk of death from malignant mammary disease, so that more intensive therapy can be used to improve survival for this group. Progress has been made in this area, and several studies identifying prognostic factors will be summarized here. The second challenge, which has been less well addressed in recent years, is to develop better treatments for aggressive mammary cancer in the dog and cat.

PROGNOSTIC FACTORS

Age, Breed, and Sex Factors

The median age of dogs with mammary tumors is 10 to 11 years. Female sex is a strong predilection factor, with mammary tumors rarely seen in male dogs (approximately 1% of malignant mammary tumors in one study were seen in males). Mammary tumors in males they tend to be highly malignant. While reproductive hormone status appears not to be related to prognosis once mammary tumors have developed, the most widely accepted risk factor for developing mammary carcinoma in the dog is the number of estrous cycles in bitches before spaying. The risk in neutered bitches for developing mammary tumors is only 12% of the mammary cancer risk for intact bitches. Bitches spayed before the first heat cycle had a relative risk of 0.05% for mammary cancer, while those with 1 heat cycle had 8%, and those with 2 or more cycles had 26% relative risk. After 2.5 years of age or 4 estrous cycles the sparing effect of ovariectomy is lost.

Tumor size is of prognostic significance. In a study of 253 dogs with mammary tumors, there was significant difference in survival between groups of dogs when primary tumors were classed as <5 cm, 5–10 cm, 11–15 cm, and >15 cm in diameter. A more recent study

confirmed this finding, with tumors of less than 3 cm diameter having significantly better prognosis than tumors greater in size. This size effect was lost if the primary tumor was associated with lymph node metastasis or vessel invasion, however.

Dogs that are obese may have poorer survival when surgically treated, but the risk of developing breast cancer in obese versus thin dogs was not clearly different, as happens in women. However, one study suggested that dogs fed low fat diets (< 39% of dietary calories derived from fat) had a significantly better prognosis for 1 year survival after surgical removal of mammary tumors, particularly if also on a high protein diet, than those dogs fed higher fat diets regardless of protein content.

Inflammatory carcinoma carries the worst prognosis of all the histologic subtypes of mammary cancer, and is generally metastatic at presentation. Dogs with inflammatory carcinoma have warm, painful tumors often associated with thickened, ulcerated skin and lymphedema in the nearest limb. This condition can mimic mastitis, and dogs may be clinically depressed with nonspecific signs of illness when affected by inflammatory carcinoma. Biopsy is warranted to distinguish infectious from neoplastic cause of this condition, but mastectomy is rarely curative in inflammatory carcinoma. If surgical resection of the primary lesion is attempted, it is common to see tumor nodules recurrent in the incision line at the time of suture removal.

FELINE MAMMARY TUMORS

Cats present with an overall more aggressive form of mammary cancer than what is seen in dogs. When a mammary mass develops in a feline patient, it is 80% to 90% likely to be malignant, with the majority of these tumors being adenocarcinomas. Median age at onset is 10 to 12 years, and Siamese cats have an increased risk of mammary tumor development, with an earlier age at onset than other breeds. Association with age at spaying has not been made for the disease in cats. Mammary carcinoma cells from cats are more likely to express progesterone receptors, and cats treated with progestational drugs are more likely to develop mammary carcinoma. Most feline mammary cancers are locally invasive and have lymphatic infiltration. Size of tumor is prognostic, in that cats with smaller tumors have longer disease-free intervals and survival times.

HISTOPATHOLOGIC EVALUATION

Several histopathology classification systems have been developed to better define the prognosis in dogs with mammary malignancies, but none is universally accepted. The pathology of these tumors is complex and tumors are heterogeneous, so exact classification of tumors can be difficult. In most studies, epithelial tumors that are more highly differentiated (those with acinus and tubule formation) and tumors with few mitotic figures and more regular nuclear size and shape are associated with a more favorable prognosis.

The most recently published classification system, reported by Kurzman and Gilbertson in 1986, seems to correlate well with biologic behavior of tumors. Using this system, tumors classified as benign with moderate to marked cellular atypia revealed dogs had a nine-fold higher risk of later developing invasive carcinoma than those with benign mastopathy without atypia. Also, this system allows for histologic staging of tumors based on extent of disease, which proved to be of prognostic value. Degree of nuclear differentiation within these histologic stages further helped to identify subsets of patients. More aggressive tumors were associated with less nuclear differentiation, and tumors with better overall prognosis tended to be those with well-differentiated nuclei. This effect of nuclear differentiation was most apparent in dogs with Histologic Stage I disease, in that recurrence rates within 2 years of mastectomy were 77%, 63%, and 40% for poorly, moderately, and well-differentiated Stage I tumors, respectively. Lymphoid cellular reactivity was a positive correlate for prognosis, in that dogs with tumors infiltrated with lymphoid cells had a threefold decreased risk of recurrence or metastasis within 2 years of surgery, as compared to dogs whose tumors failed to elicit such an immune response. The final correlate with prognosis in this study was presence or absence of lymph node involvement with carcinoma; dogs with metastasis to regional nodes had a poor prognosis, regardless of other factors.

Another classification system based on descriptive morphology of tumors in 253 surgically treated dogs, refers to "complex" tumors (mixed tumors with both secretory and myoepithelial components) and "simple" tumors (only one cell type present). These subclasses were correlated with prognosis. Patients with complex carcinomas survived better and those with simple carcinomas or sarcomas. In this study, 63% of bitches with malignant mammary tumors died or were euthanized because of recurrent or metastatic tumors within 2 years of surgery.

A large series of surgically treated dogs (320 bitches) in Great Britain reported by Bostock, was subjected to classification by histopathologic morphology and correlates with survival time were reported. Dogs with benign tumors had a median survival time of 114 weeks as compared with 70 weeks for those with carcinoma. More than half the dogs with mammary carcinoma were surgically cured, and those that were destined to die of their malignancy did so within 1 year of surgery. Of the dogs that died of cancer, the pathologic description of the tumor and degree of invasiveness was correlated with length of survival.

A common assay in human medicine detects the level of hormone receptors for estrogen and progesterone in breast tumors. In women, tumors with high levels of cellular hormone receptors tend to be better differentiated and therefore to carry a better prognosis. Also, patients with hormone receptors present on their tumors are more likely to respond to hormone therapy. In the dog, limited studies have

revealed that 50% to 60% of canine mammary tumors are positive for estrogen and progesterone receptors; as is the case in women, the better-differentiated tumors are more likely to be receptor-positive. A recent limited study revealed that dogs whose tumors expressed estrogen or a combination of estrogen and progesterone receptors had longer survivals than those dogs whose tumors expressed progesterone receptors alone, while dogs that failed to express detectable hormone receptors had the poorest survival

THERAPY

Surgery

Surgical excision is the most curative modality for treatment of local breast neoplasia. Some controversy exists as to the best form of surgical therapy. Traditionally in veterinary medicine, five surgical approaches have been used for canine mammary neoplasia, ranging from: mass excision ("lumpectomy"); removal of the affected gland (simple mastectomy); removal of the tumor, gland, intervening lymphatics and regional nodes (en bloc resection); removal of the gland and adjacent glands plus lymphatics (half chain resection); and removal of the entire chain of glands plus regional nodes (unilateral mastectomy) (Table 1). Radical or whole chain excision has been demonstrated to provide no survival advantage over excisional biopsy with 2 cm margins in the dog. Less extensive surgery is associated with less morbidity and more rapid recovery, but more extensive surgery may prevent the onset of de novo tumors by reducing remaining glandular tissue and thus may be more cost effective in the long term. More extensive surgery also allows for more thorough evaluation to detect lymphatic and venous invasion, multicentric carcinoma in situ, and the regional lymph nodes for metastatic disease.

Ovariohysterectomy has been advocated at the time of mastectomy. Traditional studies have demonstrated no advantage in terms of duration of survival, local recurrence rates or distant metastasis in dogs spayed at the time of mastectomy. However, since 50% to 60% of canine mammary malignancies have receptors for hormones (estrogen or progesterone), removal of the hormone source may be helpful for a subpopulation of cases. This hypothesis was born out in a study conducted at The University of Pennsylvania by Sorenmo et al. In this study, 145 dogs with malignant mammary tumors were analyzed retrospectively. Dogs that were spayed at any time lived significantly longer than intact dogs (median survivals 470 vs. 198 days). Twenty-two dogs were spayed at the time of mammary gland removal and these dogs had a median survival time of 563 days. Dogs that had been spayed > 2 years before the diagnosis of mammary carcinoma (N = 34 dogs) had a median survival time of 331 days. The hypothesis for this study was that tumors grown in a hormone rich environment are more likely to have hormone receptors than tumors grown in a hormone poor environment. Ovariohysterectomy concurrent with mammary gland removal would therefore have a

Table 1. Surgical Approaches for Canine Mammary Neoplasia

Tumor	Surgical Technique
<5 mm, encapsulated, moveable	Lumpectomy
Central location, one gland	Mamnectomy
Multiple adjacent glands or between glands	Regional mastectomy
Numerous tumors throughout chain	Unilateral mastectomy
Numerous tumors in both chains	Bilateral mastectomy or staged unilateral (3–4 weeks apart)
Fixed to underlying tissues	Radical mastectomy

greater impact on these dogs, and leaving dogs intact after mammary tumor removal would allow more stimulation to receptor-positive tumors with early relapse and metastasis the expected outcome. Ovariohysterectomy also prevents other reproductive tract diseases such as pyometra and ovariana neoplasia.

In cats, surgical excision is the treatment of choice for local control. Unilateral or bilateral radical mastectomy has been demonstrated to lead to longer disease-free intervals but not necessarily longer overall survival times. Cats frequently develop local recurrence after mastectomy; it is not uncommon to manage these by multiple surgeries before eventual metastasis.

ADJUNCTIVE AND PALLIATIVE THERAPY

Radiation Therapy

No published studies demonstrate the efficacy of radiotherapy in prolonging survival or preventing local recurrence for canine or feline mammary malignancy. It is very likely that local radiotherapy would prove helpful in a palliative setting for select cases, especially in inflammatory carcinoma. Further studies are indicated to evaluate the benefits of adjuvant radiotherapy in canine patients.

Chemotherapy

Chemotherapy for women with mammary carcinoma is an established treatment. Drugs that have the greatest efficacy in women are cyclophosphamide, doxorubicin, methotrexate, and fluorouracil. Note that fluorouracil is contraindicated for use in cats because of fatal neurotoxicity. In the dog, very limited information has been published to support the use of chemotherapy. Doxorubicin (30 mg/m² Body Surface Area [BSA] IV every 21 days, maximum 8 cycles of therapy) and mitoxantrone (Novantrone™, Lederle Laboratories, 5.5 mg/m² BSA IV every 21 days) have shown efficacy in inducing remission in dogs with advanced mammary cancer. Little information is available regarding the use of chemotherapy in an adjuvant (micrometastatic disease) setting in dogs. The issue of treatment of micrometastatic disease in an adjuvant setting, which might ultimately lead to cures for some patients, cannot be adequately addressed until better clinical trials of chemotherapy for gross disease have been carried out for canine and feline patients. Doxorubicin and cyclophosphamide have been demonstrated to be effective as an adjuvant therapy to palliate advanced mammary carcinoma in cats.

Hormone Therapy

The drug tamoxifen (Nolvadex™, ICI Pharma) and is useful in an adjuvant or advanced disease setting in human patients. Tamoxifen is a nonsteroidal anti-estrogenic compound, capable of binding tightly to cytoplasmic estrogen receptors. The drug has estrogenic effects in some tissues, as well as anti-estrogenic effects. The distribution of tissues responsive to the agonist effect and antagonist effect of tamoxifen appears to be different in canine patients than in human patients, which may account for a difference in the efficacy as well as in the adverse effect profile. The anticancer effect of tamoxifen in treating mammary malignancy may be mediated by mechanism other than estrogen receptor binding, including alteration in signaling through other growth factor receptors and modulation of protein kinase C activity. Thus, it is possible that even estrogen receptor negative tumors may undergo remission when treated with the drug.

Because of difficulty of performing routine estrogen and progesterone receptor assays in dog tissue, hormone therapy has not been established for treatment of canine mammary tumors. A study of tamoxifen for treatment of mammary carcinoma in 16 dogs was performed by Kitchell et al. Nine dogs were treated in an adjuvant setting with mammary tumors considered at high risk of relapse based on histologic criteria, and 7 dogs had nonresectable or metastatic disease. In this study, tamoxifen (2.5–10 mg, mean dose 0.42 mg/kg BID PO) was shown to be effective in reducing tumor burden in 5 of 7 of dogs with nonresectable or metastatic mammary carcinoma. Side effects were seen in these 16 dogs including vulvar swelling, vaginal discharge, urinary incontinence, urinary tract infection, clinical signs of estrus, mental "dullness," and partial alopecia. The most significant side effects seen were pyometras; one intact female had a closed-cervix pyometra that required surgical intervention and three recently spayed bitches had stump pyometras that were managed medically. The authors suggest that the stump pyometras occurred because of inadequate time for involution of the cells in the uterine cervix, and for that reason they recommend that dogs have been spayed at least 2 months prior to instituting tamoxifen therapy. This limited study indicates a potential role for tamoxifen therapy in the management of canine mammary carcinoma. Newer, more targeted selective estrogen receptor modulators (SERMS) have been developed in human medicine and need further exploration in veterinary medicine.